Ontario Guidelines for Drug Submission and Evaluation

Ministry of Health and Long-Term Care

September 2000

Ontario

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PART I

INTRODUCTION

The Ministry has now completed the third phase of its initiative to streamline the drug evaluation and approval process. This initiative has included efforts to harmonize processes with Health Canada, wherever possible, and to increase the transparency of Ontario's drug submission review process.

Streamlining the Ministry's drug evaluation and approval process has allowed the Ministry to concentrate its efforts on aspects of the submission review process which are more pertinent to reimbursement decisions. Increasingly, the Ministry has shifted its focus to assess the relative therapeutic value and the potential economic impact of new drug products. The Ministry's goal is to evolve its role as an active manager of its benefits, providing Ontario Drug Benefit (ODB) recipients with cost effective drug products in a timely manner.

The first two phases of the streamlining initiative, implemented in 1996 and 1997 respectively, substantially reduced submission requirements. Submission requirements were reduced from 20 to 5 for single source products and 19 to 6 for multiple source products. As well, a number of changes to the drug submission review process were introduced allowing for greater transparency and improved efficiencies at all levels. The interpretive guidelines included a detailed description of the submission review process and estimated time frames for each step in the process. Checklists and work sheets were also provided to assist manufacturers in the preparation of submissions. Concerted efforts were made to ensure that communications with manufacturers were clear, comprehensive and timely.

During the third phase of the streamlining initiative, a number of key areas were addressed:

- Continued efforts were made to harmonize processes with Health Canada and to increase transparency of the submission review process.
- A review was conducted of the Ministry's Drug Quality and Therapeutics Committee (DQTC) evaluation processes and several changes were made in order to enhance quality, efficiency and consistency in decision making.
- Drug Programs Branch operations in support of the drug submission and evaluation process were also reviewed and several operational changes were implemented in order to make more efficient use of current resources and enhance the support provided to DQTC consultants and members.
- A new electronic drug submission tracking system was introduced.
- Revisions were made to *The Ontario Guidelines for Drug Submission and Evaluation*, addressing new changes and enhancing the clarity and transparency in specific areas which have been problematic for manufacturers.

Phase III of streamlining has resulted in considerable revisions to the *Ontario Guidelines for Drug Submission and Evaluation*. While previous iterations of the guidelines provided a detailed description of the review process, the current edition has been specifically reviewed to address the most common difficulties manufacturers have encountered. The number of checklists and worksheets have been expanded in order to provide manufacturers with a guide to the areas reviewers routinely address during the evaluation of a submission.

Throughout 1999 and 2000, the Ministry worked on Phase III of the streamlining initiative with both the DQTC and Health Canada. Input also was received from a number of external stakeholders including Canada's Research-Based Pharmaceutical Companies (Rx&D), and the Canadian Drug Manufacturers Association (CDMA).

In the third phase of streamlining, a number of changes have been introduced by regulation change and others through policy change. The revised regulations came into effect on September 1, 2000 and are available on the Ministry's website (http://www.gov.on.ca/health). Below are highlights of some of the changes to the regulations and review process resulting from this phase of streamlining:

Process Changes

- Opportunity provided for manufacturers to confirm receipt of submissions by the Drug Programs Branch.
- Clarified the DQTC review process.
- Transparency increased by informing the public and health care professionals on the status of submissions and the rationale supporting DQTC and Ministry decisions.
- Appeal process clarified.

Changes for Single Source Products

- Requirement for disk copy of product monograph eliminated.
- Requirement for price list eliminated.
- Requirement for dissolution studies for additional strengths of products eliminated.
- Requirement relating to ability to supply product, and Drug Benefit Price, split into two separate requirements.
- Clinical evidence requirements clarified.
- Communication with Patented Medicine Pricing Review Board (PMPRB) enhanced.
- Optimal organization of submissions described.
- Requirements for financial impact analysis and written agreement clarified.
- Templates for financial impact analysis introduced.
- Requirements for cross licensing arrangements clarified.
- Modified the requirements for notification of change.
- Exemptions introduced for new formats.
- Requirements for new indications clarified.

Changes for Multiple Source Products

- Requirement for evidence of comparative bioavailability for Guideline A and B drugs, declared bioequivalent by Health Canada, eliminated.
- Manufacturing information required for drugs declared bioequivalent by Health Canada eliminated.
- Requirements for disk copy of product monograph eliminated.
- Product sample requirements eliminated for all drug products.
- Requirement for dissolution studies for all drug products eliminated.
- Expanded the aqueous solution exemption to a wider array of oral solutions. Eliminated the requirement for finished product specifications for aqueous solutions.
- Palatability/patient acceptance requirements eliminated for all products.
- Requirement relating to ability to supply product, and Drug Benefit Price, split into two separate requirements.
- Clarified the requirements for aqueous solutions.
- Clarified the requirements when third parties are involved.
- Modified the requirements for notifications of change.
- Requirements for additional strengths, oral solutions, parenteral aqueous solutions, and topical aqueous solutions have been modified.

Summary of Changes to the Drug Submission Regulations

Regulatory Changes	ODBA (Section 12)	DIDFA (Section 6)
Revoked		6.(1)(e) Elimination of product samples 6.(1)(g) Elimination of comparative dissolution studies. 6.(1)(i) Elimination of confirmation of patient's acceptance and palatability studies for all products
Amended	12.(1)(a) Added requirement for Drug Notification Form. 12.(1)(b) Allow communication with PMPRB. 12.(1)(d) Letter of supply and proposed Drug Benefit Price separated into two letters. 12.(1)(e) Letter of supply and proposed Drug Benefit Price separated into two letters.	6.(1)(a) Added requirement for Drug Notification Form. 6.(1)(c) Elimination of finished product specifications. 6.(1)(d.1) Letter of supply and proposed Drug Benefit Price separated into two letters. 6.(1)(h) Elimination of bioavailability studies for select drugs. 6.(3) Elimination of need for manufacturing information, bioavailability studies, master formula and palatability studies and confirmation of patient acceptance for pseudogenerics. 6.(5) Expanded exemption for other oral solutions. 6.(6) Master formula exemption for drugs declared bioequivalent by Health Canada 6.(7) Exemption for bioavailability reports for Report A and B drugs.
New	12.(3.1) Exemption of new formats of currently listed products from product specific clinical data.	

HOW TO USE THE GUIDELINES

The guidelines were developed to provide manufacturers with practical information and guidance to facilitate the submission of information to the Ministry and to provide a better understanding of the submission evaluation and approval process. Manufacturers should note that Branch staff refer to the same guidelines when assessing submissions for regulatory compliance. Close attention should be paid to the requirements to facilitate rapid screening and review. The guidelines are organized as follows:

Part I Introduction

Part II Drug Submission Review Process

This section contains the description and time frame for each step of the revised review process of the Drug Programs Branch. Manufacturers should refer to this section for information on optimal submission organization and preparation.

Part III Submission Guidelines for Drug Products

This section contains the revised interpretive guidelines to the submission requirements.

A Interpretive Guidelines – *Ontario Drug Benefit Act* (ODBA)
O. Reg. 201/96 – Section 12

A manufacturer submitting a single source drug product (i.e., a drug product or chemical entity in a particular dosage form and strength not already listed in the Formulary/CDI) for listing consideration as a benefit should refer to this section for interpretation to the regulations of Section 12 under ODBA.

B. Interpretive Guidelines – *Drug Interchangeability and Dispensing Fee Act*
(DIDFA) – Regulation 935 – Section 6

A manufacturer submitting a multiple source drug product (i.e., a different brand of an already or previously listed drug) for interchangeability consideration should refer to this section for interpretation to the regulations of Section 6 under DIDFA.

Part IV Submission Guidelines for Diabetic Testing Agents

Manufacturers of diabetic testing agents should refer to Part IV for information on the submission requirements for consideration for reimbursement under the Maximum Allowable Reimbursement (MAR) schedule.

Part V Submission Guidelines for Nutrition Products

Manufacturers of nutrition products should refer to Part V for information on the submission requirements for consideration for reimbursement under the Maximum Allowable Reimbursement (MAR) schedule.

Part VI Template Letters, Checklists and Work Sheets

Template letters, checklists and work sheets have been developed to help manufacturers make submissions under ODBA and DIDFA. Relevant template letters, checklists and work sheets are provided at the end of each section of the regulations, and in Part VI of the *Ontario Guidelines for Drug Submission and Evaluation*. All forms and templates are also available on the Ministry's website (www.gov.on.ca/health).

Part VII New Policy Directives

From time to time, notices may be posted on the website or manufacturers may receive correspondence outlining new policy directives initiated by the Drug Programs Branch. For easy reference, this section can be used for filing information relating to the drug submission review process.

THE DRUG QUALITY AND THERAPEUTICS COMMITTEE (DQTC)

The DQTC was established by Order in Council #2217/68 in 1968 as an expert advisory group to provide independent and specialized advice to the Minister of Health and the Drug Programs Branch on drug-related issues. The committee evaluates both the therapeutic value and cost effectiveness of brand drugs submitted for reimbursement under the Ontario Drug Benefit Program, and makes recommendations on the interchangeability of generic drug products. Members are selected for their technical expertise and specific knowledge. The membership is composed of representatives from medicine, pharmacy, pharmacology, epidemiology, health economics and other disciplines.

In 1997, a Sunset Review was conducted of the DQTC to re-evaluate the continued role and mandate of the Committee. One of the major recommendations of the review panel was that representation from health economics and pharmacoepidemiology should be increased to enhance the committee's focus on the value for money assessment of new drugs. Changes to the Committee membership have responded to this recommendation.

The current terms of reference of the DQTC are:

(a) to establish, maintain and apply criteria to evaluate the therapeutic value and cost-effectiveness of drug products;

(b) to recommend to the Minister those new products which should be considered for publicly funded programs, and advise the Minister of the conditions under which such products should be funded;

(c) to recommend to the Minister which drug products should be designated as interchangeable products or listed drug products for the purposes of the *Drug Interchangeability and Dispensing Fee Act*, and the *Ontario Drug Benefit Act*;

(d) on an ongoing basis, to monitor and re-evaluate drugs reimbursed by publicly funded programs with regard to their continued therapeutic value and cost effectiveness;

(e) based on the best available evidence, provide advice on relevant pharmaceutical and therapeutic issues to the Ministry of Health and Long-Term Care;

(f) at the Minister's request, act as liaison between the Minister and other professional groups;

(g) to contribute and support Ministry efforts on education about drugs and related issues.

The DQTC also provides recommendations to the Ministry, on a case by case basis, about coverage on thousands of requests received each year for drugs not listed in the Formulary/CDI through the Individual Clinical Review (Section 8) mechanism. A comprehensive roster of consultants/reviewers has been established to assist the DQTC in the review of drug product documentation and other drug-related issues. The services of these consultants/reviewers are obtained to complement the expertise available on the DQTC.

Only complete submissions (i.e., those which satisfy all the regulatory requirements under ODBA or DIDFA) undergo a review by the DQTC. The DQTC considers several factors during its review, including objective evidence of safety and efficacy in comparison to listed alternatives, and evidence supporting the cost effectiveness of new products.

INQUIRIES AND ASSISTANCE

Inquiries and correspondence on this publication should be directed to:

Director
Drug Programs Branch
Ministry of Health and Long-Term Care
3rd Floor, 5700 Yonge Street
Toronto ON M2M 4K5

Telephone: (416) 327-8109
Fax: (416) 327-8123

Email: drugprograms@moh.gov.on.ca

Web: www.gov.on.ca/health

PART II

DRUG SUBMISSION REVIEW PROCESS

In 1974, the Ministry of Health and Long-Term Care (Ministry) established the Ontario Drug Benefit Formulary/Comparative Drug Index (Formulary/CDI) for recipients eligible for benefits under the Ontario Drug Benefit (ODB) program. The Ministry routinely publishes the Formulary (the list of benefits provided under the *Ontario Drug Benefit Act*) and the Comparative Drug Index (the list of interchangeable drug products designated under the *Drug Interchangeability and Dispensing Fee Act* (DIDFA)). These two lists are published as one book referred to as the "Formulary/CDI". Approximately four updates are published throughout the year to incorporate changes to listings and drug prices.

In order to be considered for reimbursement through the Formulary/CDI under the ODB program, submissions are accepted for consideration when they comply with the following regulations:

- *Ontario Drug Benefit Act (ODBA)* – O. Reg. 201/96 – Section 12 for single source or brand name products; or

- *Drug Interchangeability and Dispensing Fee Act (DIDFA)* – Regulation 935 – Section 6 for multiple source or generic products.

The following sections A. through L. describe each step of the review process in detail. The flow diagrams in Section L outline in general terms the drug submission review process from the time a submission is received by the Ministry to the time a decision is made to list a drug product. They describe the flow of information through the Ministry and government, as well as the communication between the Drug Programs Branch and pharmaceutical manufacturers.

A. Filing of Drug Submissions
B. Screening of Drug Submissions for Regulatory Compliance
C. First DQTC Review
D. Second DQTC Review
E. Fast Tracking Mechanism
F. Order of Submission Consideration by the DQTC
G. Withdrawal Process
H. Written Agreement
I. Regulatory Process
J. Time Frames
K. Meetings with Manufacturers
L. Summary of Manufacturer Options After Negative First and Second Reviews

A. FILING OF DRUG SUBMISSIONS

A manufacturer who wishes to have a drug product considered for listing in the Formulary/CDI should file a submission with the:

Director
Drug Programs Branch
Ministry of Health and Long-Term Care
3rd Floor, 5700 Yonge Street
Toronto ON M2M 4K5

Communication during the Submission Process

All documentation for new drug submissions, correspondence regarding listed drug products or any other drug-related matters, including program management initiatives, must be directed to Drug Programs Branch, and not to the Ministry's expert advisory committee, the Drug Quality and Therapeutics Committee (DQTC), its chair, or any members or consultants to the committee.

Direct approaches (in any form) to DQTC members, in their capacity as members of the committee, may be viewed as introducing a conflict of interest and might create an appearance of bias or unfairness on the part of committee members. Although the identities of committee members are in the public domain, the identities of DQTC reviewers are not revealed and are held in confidence by the Ministry.

Direct contact by a manufacturer with a DQTC member or DQTC consultants/reviewers may result in a delay in the decision about the product in order to arrange for an unbiased recommendation of the product.

Written Communication

The Ministry acknowledges all submissions received from manufacturers in writing. All written communication between the Ministry and a manufacturer takes place through a single primary contact. The Ministry will also send a copy of all submission-related correspondence to the most senior company official (e.g., president/CEO) of each company. The Ministry requires written notification in order to change the primary company contact, or any other information related to contact information (e.g., address, telephone number.)

Submission Conditions Prescribed Under Regulations

A submission must follow either the conditions prescribed under O. Reg. 201/96 made under the *Ontario Drug Benefit Act* (ODBA), or the conditions prescribed under Regulation 935 made under the *Drug Interchangeability and Dispensing Fee Act* (DIDFA).

i) A submission for a single source product (i.e., a drug product or chemical entity in a particular dosage form and strength not already listed in the Formulary/CDI) must meet the requirements of O. Reg. 201/96 under ODBA. A single source product submission includes a request to:

- list a new chemical entity or a new single-source drug product in the Formulary/CDI;
- add a new strength of a product or a new dosage form to the Formulary/CDI;
- add a new indication for a product to the Formulary/CDI;
- relist a single source product which was previously removed from the Formulary/CDI.

ii) A submission for a multiple source product (i.e., a different brand of an already listed drug product) must meet the requirements of Regulation 935 under DIDFA. A multiple source submission includes a request to:

- designate a new multiple source product as interchangeable;
- add a new strength of a multiple source or a new dosage form to the Formulary/CDI; and
- redesignate a multiple source product as an interchangeable product.

Only complete submissions (i.e., those that meet all regulatory requirements under ODBA or DIDFA) will be eligible for review and consideration for listing/ interchangeability designation. The date a submission is deemed complete determines the subsequent ranking of the product versus another in the review process.

Although the submission requirements must be met in order to initiate the review process, the Ministry reserves the right to request additional information needed to address any uncertainties associated with a submission or to resolve questions which may have arisen. The Drug Programs Branch or DQTC may request additional information from manufacturers at any time during the review and/or screening process. **Manufacturers are encouraged to respond to these requests in a timely manner to avoid delays in the submission review process. Manufacturers are free to withdraw their submission at any time.**

Format and Organization of Submissions

The following section offers a number of suggestions to manufacturers to prepare submissions more effectively.

A cover letter and a table of contents should accompany the submission. The cover letter should clearly state:

- the brand name, generic name, strength, dosage form (including the various package sizes to be considered for reimbursement consideration);
- the regulation under which the submission is being made (either the *Ontario Drug Benefit Act* or the *Drug Interchangeability and Dispensing Fee Act*);
- if submitted under the *Drug Interchangeability and Dispensing Fee Act,* the name of the original product to which an interchangeability designation is being sought.
- The type of listing requested (e.g., General Benefit, Limited Use)
- any exemptive regulations being applied for (e.g., additional strength, format, pseudogeneric or aqueous solution);
- a fast-track request, if applicable (refer to Section E: Fast Tracking Mechanism).

A "Submission Summary" template has been developed to assist manufacturers in providing the requested information. In addition, various template letters, work sheets, tables and other summaries have been developed to ensure that all relevant questions have been addressed. Manufacturers may wish to refer to the documentation found in Part VI: Template Letters, Checklists and Work Sheets or to the Ministry's website for copies of these documents.

All submissions must be well organized and indexed. Binders should be sturdy and not overfilled. Manufacturers should restrict individual binders to a maximum 7.2cm (3 inch) width. Duplexed (double sided) pages are preferred. In order to organize a submission in a manner that will facilitate review, submissions should be clearly tabbed according to the relevant section of the requirements. **Three separate sets of the entire submission must be provided for single source submissions, and two sets must be provided for multiple source submissions, diabetic testing agent submissions, and nutritional product submissions.**

In order to facilitate the review of a more complex product where multiple reviewers may be engaged, the Drug Programs Branch may request additional copies of a submission. While not required to do so, manufacturers are advised that the Drug Programs Branch can experience delays when requesting reproduction of large submissions documents internally, especially those submissions which contain a large number of inserts and attachments. Due to space constraints, additional or extra copies of a submission should not be forwarded **unless specifically requested**.

Any documentation in a foreign language should be translated into one of Canada's official languages, preferably English.

An incomplete submission does not enter the DQTC review process until all the required information is received. Disorganized or incomplete submissions may be returned at the discretion of the Ministry, at the manufacturer's expense, without prejudice to refiling.

Transparency

The Ministry continues to make efforts to increase the level of transparency of the submission process. In 1996, a number of measures were introduced which increased the frequency and nature of communications with manufacturers about their submissions during the course of the review process. **To better inform the public and health care professionals, the status of submissions and the rationale supporting DQTC and Ministry decisions will now be released.** In addition, to further increase the level of transparency for manufacturers, technical portions of the reviewer's reports may be released to the submitting manufacturer. All other submission information will continue to be held in confidence by the Ministry.

Challenges to a Competitor's Product

If a manufacturer has concerns about a competitor's submission or product listing, the Ministry will accept any information that the manufacturer believes is relevant to the consideration of the competitor's product. All objections and information must be clearly documented and provided in writing to the Ministry. Verbal concerns from manufacturers will not be considered nor taken forward to the DQTC for consideration. Two copies of the entire challenge should be supplied to the Branch. **Any information provided by a manufacturer regarding a competitor's product will be shared in whole or in part with the competitor for their consideration and comments, at the discretion of the Ministry and without further notification from the Ministry.**

B. SCREENING OF DRUG SUBMISSIONS FOR REGULATORY COMPLIANCE

Submission Receipt and Review

Each drug submission is date stamped when it is received by the Drug Programs Branch.

Manufacturers may confirm receipt of a submission by calling the Drug Programs Branch at (416) 327-8109. Calls should be made by the Ministry's primary contact, as described in Section A: Filing of Drug Submissions. Reception will transfer these calls to an available submission coordinator. The submission coordinator will only provide information regarding the receipt of a submission. Submission coordinators are not able to address other issues relating to the evaluation process.

A submission is screened for regulatory compliance by Drug Programs Branch staff according to the date of receipt. The targeted time frame for this step is approximately two weeks from the date the submission is received by the Drug Programs Branch. This time frame may be prolonged during periods of resource constraints. If a submission satisfies all the regulatory requirements, it is considered to be **COMPLETE.** If a submission does not satisfy all the regulatory requirements, the submission is considered to be **INCOMPLETE** and will not progress through the review process.

Communication to Manufacturer

Once a submission is screened, a Notice of Drug Submission Status (NDSS) is issued. The NDSS will indicate the status of the submission (Complete or Incomplete) as well as the assigned file numbers. Each submission is assigned a unique master file number, and each individual drug product within the same submission is assigned a unique drug product number. The NDSS for an incomplete submission will state the reasons why the submission was deemed incomplete.

Manufacturer's Response

A manufacturer should make reference to the master and drug product file numbers in all subsequent correspondence to the Drug Programs Branch.

If a manufacturer receives a NDSS which indicates that the submission was deemed incomplete, the manufacturer will be offered a **two-month** period in which to complete the submission. The letter accompanying the additional information should make reference to the assigned file numbers and refer to the regulatory deficiencies. The package should be submitted as stated in Section A: Filing of Drug Submissions.

An incomplete submission will be automatically withdrawn if a manufacturer fails to provide all the requested information within two months from the issue date of the NDSS. **The original submission will be destroyed at that time, without prejudice to refiling.**

Ministry staff screen additional information submitted (e.g., resulting from an "incomplete" NDSS letter) in the same sequence as all other submissions received. As noted above, the targeted time frame to screen this information is approximately two weeks.

When all the regulatory requirements are satisfied, a submission is deemed complete and enters the review process. **Any additional, unsolicited documents should not be submitted, as they will not be forwarded to DQTC reviewers for consideration.**

Guideline A and B Multiple-Source Submissions

A portion of multiple-source submissions filed under the Drug Interchangeability and Dispensing Fee Act (DIDFA) – Regulation 935 – Section 6 will no longer receive DQTC review as described in Sections C and D: First DQTC Review and Second DQTC Review, respectively.

For these submissions, drug products that have been designated as complete will proceed automatically to the next stage in the evaluation process.

For additional information on this exemption, please refer to DIDFA - Regulation 935 Section 6.(7) and the corresponding section in Part IIIB of these guidelines.

C. FIRST DQTC REVIEW

Once a submission is determined to comply with the regulations, its status is noted as complete and the submission is sent to one or more DQTC reviewers. Submissions are reviewed by DQTC members and/or by reviewers drawn from a roster of external consultants. The targeted time frame for the reviews is four weeks. During this period the status of the submission is considered “Under Review”.

Submissions that are considered complex by DQTC reviewers or by the Ministry may require additional time to review. Occasionally, a panel or subcommittee of the DQTC may be asked to review a specific submission which may extend the timeline for the DQTC review.

When all reviews have been received by the Ministry, the status of the submission changes to “Review Complete”. The submission is then scheduled as a **First Review** agenda item for the next available DQTC meeting, and ranked in the meeting agenda according to the date the submission was deemed complete by the Ministry.

DQTC Recommendation

At the next available DQTC meeting, the committee as a whole discusses each submission, with occasional input from the reviewers, other expert external consultants, and the Ministry. The DQTC has a number of options in making a recommendation regarding a product, including:

- general listing
- limited use listing
- reimbursement through a pre-approval mechanism, Section 8:
  - individual clinical review
  - expedited review with criteria
- facilitated access
- no reimbursement under any circumstances.

Different drug products in the same submission may receive differing recommendations, based on the DQTC’s assessment.

For complex products, once a recommendation has been made by DQTC for Limited Use or Section 8, a subcommittee may be asked to formulate the specific criteria. In such cases, there will be a longer time frame before criteria for reimbursement are issued to the manufacturer.

The committee's recommendations are drafted into minutes which are generally ratified by fax within 14 days of the DQTC meeting. Minutes pertaining to complex issues/products may be ratified at the subsequent meeting of the DQTC. The ratified minutes form the basis of communication to the manufacturer regarding the submitted drug product.

Communication to Manufacturer

A further NDSS is issued to a manufacturer after the DQTC review. Where the DQTC has rejected a product for listing, the issues or concerns raised by the DQTC are summarized in the NDSS. The NDSS is generally faxed within five days of when the DQTC minutes are ratified. Great effort is taken by the DQTC and the Ministry to be clear and comprehensive to aid the manufacturer in preparing a response.

Where the DQTC has recommended a product for listing/reimbursement, the NDSS will state the proposed reimbursement status and that the product will proceed to the next stage in the evaluation process. Alternatively, it may provide details of the reimbursement criteria to be applied through Section 8. In the same NDSS, the manufacturer may be requested to confirm the DIN and pricing information for the recommended drug product. At this time, the manufacturer should also confirm the correct name, strength, dosage form and package size of the drug product. The manufacturer may be requested to provide a written agreement for a single source product, as outlined in Section H: Written Agreement.

A positive recommendation is **not** a guarantee of listing in the Formulary/CDI. Recommendations made by DQTC are subject to review and decisions made by the Ministry and the government. The NDSS may or may not indicate the approximate timing of the next Formulary/CDI update. Due to regulatory and legislative requirements, the Ministry's internal cut-off date for a specific Formulary/CDI precedes the date of the actual update by ninety days or more. Formulary/CDI updates are generally produced on a quarterly basis.

Manufacturer's Response

When responding to a negative recommendation, the manufacturer must provide a cover letter clearly indicating the submission's master and product file numbers and the questions being addressed. Manufacturers should respond directly to the DQTC concerns raised in the NDSS. Instances where the DQTC recommends a Limited Use listing are not considered negative recommendations. However, manufacturers can request reconsideration of a Limited Use recommendation in the same manner.

The response should be addressed to Drug Programs Branch as outlined in Section A: Filing of Drug Submissions. Three copies must be provided for single source submissions, and two copies must be provided for multiple source submissions. Manufacturers may not send information directly to DQTC members and reviewers. Direct communication with a DQTC member/reviewer may introduce a conflict of interest, and will result in delays of the handling of the submission as outlined in Section A: Filing of Drug Submissions.

D. SECOND DQTC REVIEW

A manufacturer is provided with six weeks from the date of issue of the NDSS to respond to the DQTC's concerns or issues, in order to maintain the submission's existing review ranking. Three copies must be provided for single source submissions, and two copies must be provided for multiple source submissions, diabetic testing agent submissions, and nutritional product submissions. If the manufacturer meets the six-week deadline, then the product will be reviewed by the DQTC following the process outlined in Section C. If the manufacturer fails to meet the deadline, then the product loses its ranking and will be considered only as the DQTC agenda permits.

Reviewers are provided with four weeks to consider a manufacturer's response and file their reports with the Ministry. During this period the status of the submission is considered "Under Review". For a complex product, a subcommittee meeting may be arranged/ reconvened before the discussion takes place by DQTC as a whole.

Once all the reviews have been received by the Ministry, the status of the submission changes to "Review Complete" and the submission is scheduled as a **Second Review** agenda item for the next available DQTC meeting.

DQTC Recommendation

At the next available DQTC meeting, the DQTC as a whole discusses each submission, with input from the reviewers, other external consultants, and the Ministry.

The committee's options in making a recommendation as well as the process by which recommendations are drafted into minutes are described in Section C: First DQTC Review.

Communication to Manufacturer

Once the minutes are ratified, the manufacturer is notified of the DQTC recommendation in a further NDSS. A positive recommendation is issued if the DQTC is satisfied with the manufacturer's response to the issues raised in the first review. Where a product is recommended for listing, the manufacturer is requested to confirm the DIN and price, and may be requested to provide a Written Agreement.

However, if the DQTC determines that the requested information does not adequately address all of DQTC concerns from the first review, then a negative recommendation is issued. At this point, the submission loses its ranking in the submission review cycle.

Manufacturer's Response

The manufacturer will be offered a six month period to respond to a second negative recommendation. If a response is received during this time frame, the submission will be reconsidered by the DQTC, as the agenda permits. Three copies must be provided for single source submissions, and two copies must be provided for multiple source submissions. If a manufacturer fails to address the outstanding issues within a six month time period, the submission will be **withdrawn** and subsequently destroyed.

E. FAST TRACKING MECHANISM

Drug products may be considered for review on a "fast track" basis if the complete submission is for:

- new chemical entities that represent new drugs effective for the treatment of immediately life-threatening diseases and other serious diseases where no comparable drug is marketed in Canada; or

- new drug products that will have a significant impact in reducing Ontario's Ministry of Health and Long-Term Care expenditures ***(more than $1,000,000 in savings per year)***, or drug products that offer significant savings ***(more than 35% and at least $250,000 per year)*** to the Ontario Drug Benefit program.

The decision as to whether a submission will be "fast tracked" will be made by the DQTC Chair and Drug Programs Branch staff, with expert consultation as required. Manufacturers should clearly indicate if they are requesting "fast tracking" consideration in the submission cover letter, and should provide documentation to demonstrate eligibility. Submissions that do not contain adequate justification for "fast tracking" will not be considered for this mechanism. A drug product will be automatically scheduled for regular review if the decision is made not to "fast track".

Drug products designated for "fast tracking" are screened by the Ministry on a priority basis and will be given a preferred status on the DQTC agenda. A "fast-track" submission must continue to meet all submission regulatory requirements before entering the DQTC review process.

F. ORDER OF SUBMISSION CONSIDERATIONS BY THE DQTC

First review submissions, both single source and multiple source, are considered first on the DQTC meeting agenda. After first review submissions, second review submissions and finally reconsideration submissions are considered on the DQTC meeting agenda. Within each category (first review, second review, reconsideration), submissions are ranked in the agenda according to the date each submission was deemed complete. Drug products designated for "fast tracking" will be given a preferred status.

G. WITHDRAWAL PROCESS

A submission may be withdrawn from the review process voluntarily by the manufacturer. At any time throughout the review process, a manufacturer may withdraw a submission by providing a written request to Drug Programs Branch. When this letter is received by the Drug Programs Branch, the submission will be destroyed.

The Ministry may also withdraw the submission from the review process if the manufacturer does not sufficiently address:

- regulatory deficiencies in the Notice of Drug Submission Status (NDSS) within **two months** of the issue date of the latest NDSS; or

- DQTC concerns within **six months** of the date of the latest NDSS.

Submissions that have been withdrawn by the Ministry will be destroyed. The Ministry may retain certain portions of the submission for its records.

H. WRITTEN AGREEMENT

An amendment under the *Ontario Drug Benefit Act*, Section 12.0.1 of O. Reg. 201/96, effective June 1, 1998, introduced written agreements as a condition of listing for all new single source products recommended for listing in the Formulary/CDI.

The manufacturer of the product(s) must enter into a written agreement with the Ministry, which includes the net forecasted costs (excluding up-charge and professional fee) to the province in the three-year period commencing the day the product is listed.

The Ministry encourages manufacturers to submit a written agreement at the time a drug submission is filed. A written agreement is required from the manufacturer after a positive DQTC recommendation is made, if it has not yet been provided.

To assist manufacturers, the Ministry has developed a template letter to be used for this purpose. Copies are also available in Part VI of these guidelines, and on the Ministry's website. If manufacturers choose to use the template, they should ensure that it is printed on company letterhead, dated and signed by an appropriate senior company official.

It is Ministry policy that a written agreement is also required when a product changes from a Limited Use to a general benefit listing.

For additional information, refer to regulation 12.0.1(1) and the accompanying section in Part IIIA of these guidelines.

Review of Manufacturer's Written Agreement

Once a new single source drug product has been reviewed and recommended by the DQTC for listing in the Formulary/CDI, Ministry staff review the written agreement submitted by the manufacturer and evaluate the forecasted net ODB cost of the product for the three-year period.

Review of the net impact on ODB expenditures is based on: the recommended conditions for reimbursement (in the case of Limited Use drugs); current utilization of similar products in the same therapeutic category; potential utilization of the new product with consideration of the target population; potential market share; replacement products; duration of therapy; average dose; and, the manufacturer's forecast and assumptions. Specifically, the evaluation includes the following considerations:

1. Size of the potential market and where applicable, current utilization trends for the same category of drugs.

2. Potential market share of the new product and the impact of the proposed price relative to other products on the Formulary/CDI.

3. Potential for use outside appropriate areas covered in the forecast assumptions (e.g., if a Limited Use listing is recommended, the forecast assumptions should be consistent with the Limited Use criteria).

4. Contribution to more efficient/cost effective use of other health services.

5. Comparison of the forecast and assumptions of the manufacturer in relation to that of the Drug Programs Branch.

6. Other available information where applicable (e.g., information contained in the manufacturer's submission/forecast).

An agreement is required between the manufacturer and the Ministry on the forecasted net costs of the product(s) to the Ministry before the Ministry can make the recommendation to list the product in the next update to the Formulary/CDI. If the Ministry accepts the forecasted costs provided in the written agreement, the product is referred to government for consideration for listing in a future update to the Formulary/CDI. If the Ministry has concerns with the forecasted costs provided in the written agreement, the manufacturer is notified. The manufacturer and Drug Programs Branch staff may meet to discuss the forecasted costs in the written agreement and the underlying assumptions.

I. REGULATORY PROCESS

Formulary/CDI updates are implemented by regulation. Drug products, which successfully complete the steps noted above and are recommended for Formulary/CDI listing, are compiled into a submission and taken forward for senior Ministry approvals. Since any changes to the Formulary/CDI will have a financial impact on the provincial budget, all Formulary/CDI additions must be approved by the Management Board. Approvals are also sought from the Statutory Business Committee before being presented to Cabinet for approval, signed by the Lieutenant Governor in Council and filed. Generally, the latter steps are handled within the same week. Manufacturers are notified immediately in writing of the disposition of their submissions when a new regulation is filed. The regulatory changes are incorporated into the Formulary/CDI or as an update to the Formulary/CDI. Details of new listings are posted on the Ministry's website. In addition, a bulletin board message is issued to all pharmacies. Manufacturers interested in receiving email copies of bulletin board messages communicated to pharmacies should contact the Drug Programs Branch at: **drugprograms@moh.gov.on.ca**.

J. TIME FRAMES

The estimated time frames for each step of the review process have been provided in an effort to increase the transparency of the review process to manufacturers. Manufacturers can track their submissions by understanding the process and tracking the correspondence they receive from the Ministry. This should help manufacturers to determine when they should next expect a communication from the Drug Programs Branch and the deadlines for responses.

Drug Programs Branch Activities	Targeted Time Frame
Branch screening of submission	two weeks
DQTC review of submission	four weeks
DQTC recommendation	two to four months from the date a submission is deemed complete
DQTC reconsideration	As DQTC agenda permits – usually same as for initial review
Notice of final acceptance	2-4 weeks prior to the effective Formulary/CDI listing date

Manufacturer Activities	Time Frame
Filing a submission	None – **complete** submissions are reviewed on a continuous cycle
Response to an initial "Incomplete" NDSS	**two months** from the date of issue of the NDSS
Response to a first negative recommendation NDSS.	**six weeks** from the date of issue of the latest NDSS with a negative recommendation to maintain consideration as a second submission; **six months** from the date of issue of an NDSS with a further negative recommendation, to be considered as a reconsideration submission.
Response to the second negative recommendation NDSS.	**six months** from the date of issue of a NDSS with a second negative recommendation. The submission will be considered as a reconsideration submission.

NDSS = Notice of Drug Submission Status.

K. MEETINGS WITH MANUFACTURERS

Manufacturers may request a meeting with members of the DQTC and/or Ministry staff to discuss their drug submissions. Meetings with DQTC can be arranged at any time, however, they are encouraged only in those exceptional circumstances where manufacturers are unable to address the issues raised by the DQTC through the submission of additional written information. Meetings with Ministry staff may be requested if a manufacturer remains unclear on the reasons for DQTC rejection, or remains uncertain about the necessary steps required to overcome the objections of the DQTC. Following a meeting, a manufacturer may decide whether to accept a negative recommendation, withdraw the submission, or respond in writing for DQTC consideration.

Depending on the number of meeting requests, meetings with Ministry staff or the DQTC are unlikely to be scheduled within the initial six week response period to maintain review ranking. This may be an important factor in a manufacturer's decision whether to request a meeting, as review ranking may be lost.

A meeting with the DQTC before a submission is filed or received is not possible. The earliest a meeting with the DQTC should be requested is after the first negative recommendation from the DQTC. Manufacturers may also request reconsideration of a Limited Use recommendation. Manufacturers should provide a written notice to the Drug Programs Branch, requesting a meeting with the DQTC and the Ministry, stating the purpose and agenda of the meeting. The allocated time for meetings (generally forty-five minutes in duration) is strictly adhered to in order to accommodate all meeting requests from manufacturers. Manufacturers should have a clear agenda and use the allocated time in their best interest. Manufacturers may provide a short presentation, but the majority of the time should be used as a discussion forum where manufacturers can clarify DQTC's concerns about a specific drug product.

Presentation materials intended for distribution at a meeting with DQTC should be forwarded to the Ministry at least two weeks prior to the meeting date. Manufacturers should clarify the number of copies required with Drug Programs Branch staff at (416) 327-8109 before forwarding any material.

L. SUMMARY OF MANUFACTURER OPTIONS AFTER NEGATIVE FIRST AND SECOND REVIEWS

If the manufacturer chooses not to respond to a negative recommendation after a first review, within the six week time limit, or if they are in receipt of a second negative recommendation, the drug product will no longer maintain its existing rank in the review cycle. If six months has elapsed since a negative recommendation was issued, the manufacturer should file a new submission. However, within a six-month time frame, the manufacturer may consider one of several options described below.

Option 1 – Reconsideration

A manufacturer may provide additional information in response to a negative recommendation. Although the drug product will no longer have its original submission ranking, the submitted information will be reviewed by external reviewers and scheduled for the next available DQTC meeting, as the meeting agenda permits.

Option 2 – Meeting

A manufacturer may request a meeting to discuss any outstanding issues/concerns, as outlined in Section K: Meetings with Manufacturers. Requests for a meeting should be made in writing to the Drug Programs Branch. Meetings with Ministry staff, as well as meetings with representatives of the DQTC may be arranged at the request of the manufacturer. The same conditions that apply in the case of a request for a meeting after the first negative recommendation apply after the second.

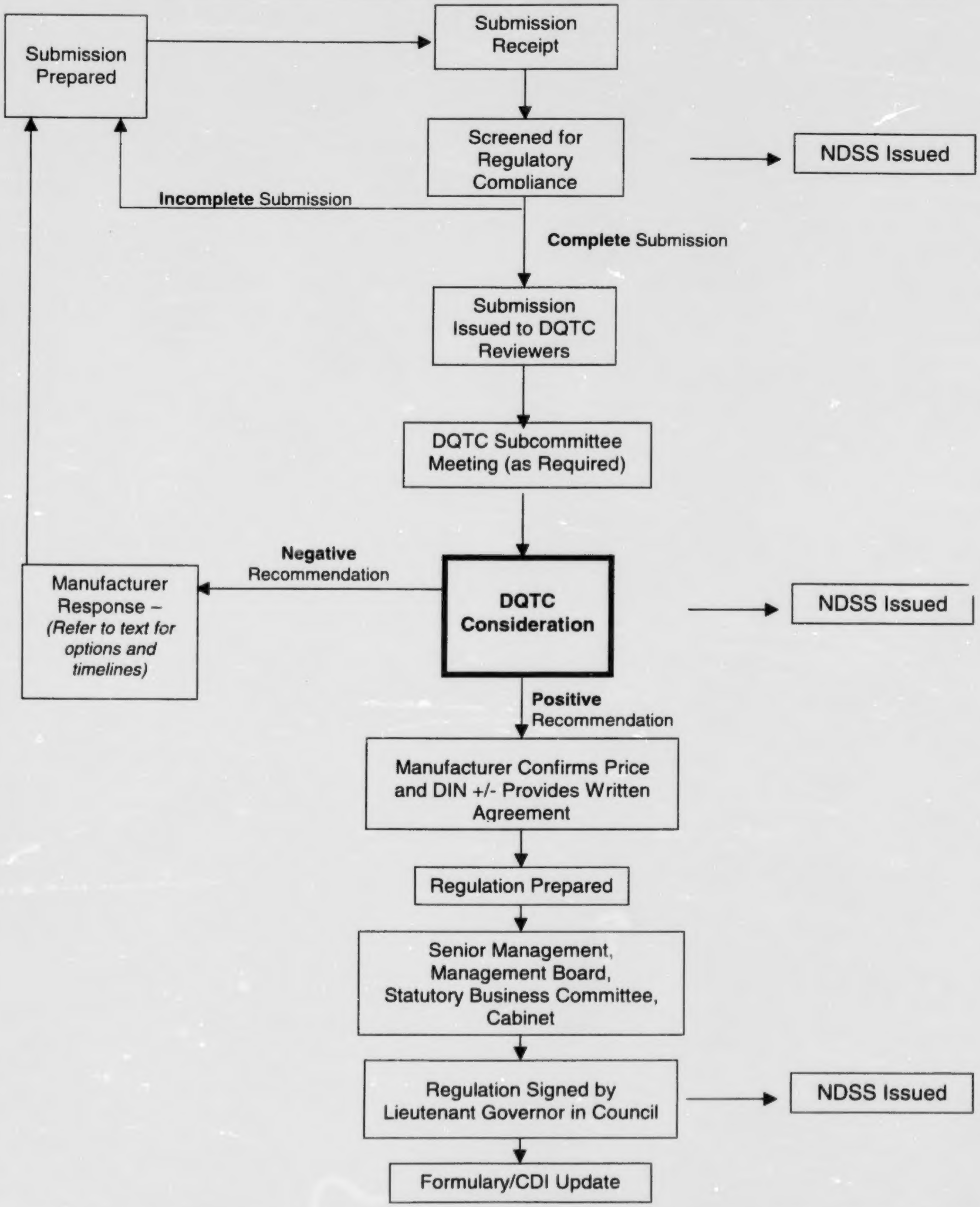
Any new information should still be submitted to the Drug Programs Branch and it will be considered by the DQTC along with the outcomes of the meeting. Although the drug product will lose its ranking in the review cycle, it will be scheduled for review at the next available DQTC meeting, as the agenda permits.

Option 3 – Withdrawal

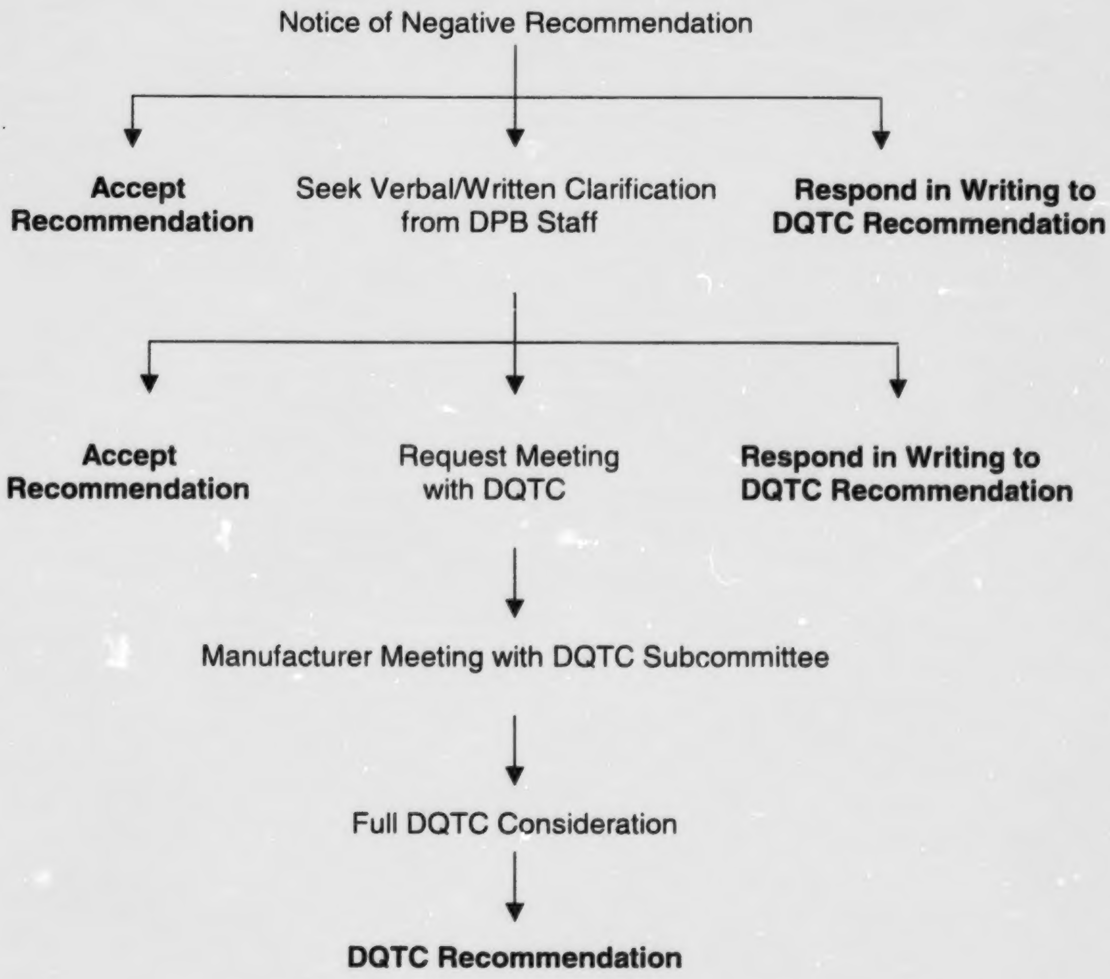
At any time in the review process, a manufacturer may withdraw a submission by providing a written request to the Drug Programs Branch. Upon receipt of the request, the Ministry will destroy the submission, without prejudice to refiling.

The flowcharts on the following pages outline the submission review process and outline options available to manufacturers after a negative recommendation from DQTC.

Submission Consideration Process


Submission Prepared
Submission Receipt
Screened for Regulatory Compliance
NDSS Issued
Incomplete Submission
Complete Submission
Submission Issued to DQTC Reviewers
DQTC Subcommittee Meeting (as Required)
Negative Recommendation
Manufacturer Response – (Refer to text for options and timelines)
DQTC Consideration
NDSS Issued
Positive Recommendation
Manufacturer Confirms Price and DIN +/- Provides Written Agreement
Regulation Prepared
Senior Management, Management Board, Statutory Business Committee, Cabinet
Regulation Signed by Lieutenant Governor in Council
NDSS Issued
Formulary/CDI Update

Process for Clarifying or Requesting a Reconsideration of a DQTC Recommendation


Notice of Negative Recommendation
Accept Recommendation
Seek Verbal/Written Clarification from DPB Staff
Respond in Writing to DQTC Recommendation
Accept Recommendation
Request Meeting with DQTC
Respond in Writing to DQTC Recommendation
Manufacturer Meeting with DQTC Subcommittee
Full DQTC Consideration
DQTC Recommendation

PART III

SUBMISSION GUIDELINES

FOR

DRUG PRODUCTS

These guidelines are designed to help drug manufacturers make product submissions to the Ministry of Health. They describe the information required to comply with:

- Section 12 of O. Reg. 201/96 under the *Ontario Drug Benefit Act (ODBA)*; and
- Section 6 of Regulation 935 under the *Drug Interchangeability and Dispensing Fee Act (DIDFA).*

Drug product submissions that meet the regulatory requirements of the ODBA will be considered for listing in the Ontario Drug Benefit Formulary/CDI. Product submissions that meet the regulatory requirements of the DIDFA will be considered for designation as an interchangeable drug.

When reviewing a drug product submission, the Ministry or the DQTC may request additional information.

These guidelines were developed by the Drug Programs Branch. They are not intended to be a comprehensive interpretation and should be used in conjunction with the appropriate acts and regulations.

PART III A

INTERPRETIVE GUIDELINES

FOR

ONTARIO DRUG BENEFIT ACT

O. Reg. 201/96, SECTION 12

A drug product may be considered for listing in the Formulary/Comparative Drug Index (Formulary/CDI) when the submission meets the following requirements under the *Ontario Drug Benefit Act*:

12.(1)(a) evidence of Health Canada's approval:

- Notice of Compliance; and
- Drug Notification Form; and
- product monograph; and

12.(1)(b) consent letter allowing communication with Health Canada, other provinces/territories and the Patented Medicine Prices Review Board; and

12.(1)(d) proposed Drug Benefit Price; and

12.(1)(e) letter confirming ability to supply anticipated demand for product at Drug Benefit Price; and

12.(1)(h) clinical evidence; and

12.(1)(i) pharmacoeconomic evidence; and

12.0.1 written agreement.

The interpretations for each of these regulations are outlined on the following pages; where necessary, points of clarification and details related to specific applications are also provided. Similar information is provided for regulations 12.(2) through to 12.(6) which deal with various exemptions to the regulations above, and for regulation 12.1 which outlines the conditions for a listed product to continue to be designated as a listed product.

To assist the manufacturer in preparing a submission, various template letters, tables, checklists, work sheets and summaries have been provided; copies of these templates are also available in Part VI and on the Ministry website (www.gov.on.ca/health).

Note: Over the last few years, several regulations (e.g., 12.(1)(c)) have been revoked and therefore no longer appear in the list above; also, some regulations have been renumbered.

12.(1) A strength and dosage form of a drug product shall not be designated as a listed drug product unless the manufacturer of the drug product submits to the Minister,

Interpretation

This section applies to a request to:

- list a new chemical entity or a new single source product in the Formulary/CDI;
- add a new strength of a product or a new dosage form to the Formulary/CDI;
- add a new indication for a product to the Formulary/CDI;
- add a new format of a drug product
- relist a single source product which was previously removed from the Formulary/CDI.

Points of Clarification

The Ministry acknowledges all submissions received from manufacturers in writing. Please note that only complete submissions (i.e., those that satisfy all the regulatory requirements) will be considered for listing. The date a submission is deemed complete determines the subsequent ranking of the product versus another in the review process.

New Indications

In addition to submissions for new listings in the Formulary/CDI the Ministry will accept submissions for new indications of products which are already listed. The requirements for these submissions have not been defined by regulation; however, manufacturers are encouraged to provide the following in order have their submission considered:

- evidence of Health Canada's approval of the indication;
- consent letter authorizing communication with Health Canada, provinces, and PMPRB;
- clinical and pharmacoeconomic evidence, including the relevant checklists. The clinical data should be product specific.;
- budget impact as it relates to the written agreement.

Third Party Involvement

The manufacturer named on the Notice of Compliance (NOC) or Drug Notification Form (DNF) who is responsible for the product in Canada can file a submission with the Ministry. It is possible that a party other than the manufacturer named on the NOC/DNF may file a submission. It is also possible that a third party may be involved with a submission in other ways (e.g., product manufacturing). Where the third party assumes the right to distribute and sell a drug, they will be considered to assume responsibility for the product and certain confirmations will be necessary from that third party. Where the third party acts as an agent only, on behalf the NOC holder, all of the confirmatory documentation will be required from the NOC holder.

Under these circumstances, additional documentation will be necessary to clearly establish the relationship of the third party with the holder of the NOC, the relationship between any different drug products referred to in the submission, and to ensure that all requirements are met. The submission will not be deemed complete unless sufficient documentation of all aspects of the submission and the relationships between all parties and drug products are provided and well understood. The listing in the Formulary/CDI will list the name of the manufacturer holding the NOC.

The requirements related to third party involvement have not been defined by regulation; however, when a third party is involved in a submission, the following documentation should be provided:

- **Product Confirmation Letter -** A letter from the NOC holder dated and signed by a senior company official confirming that the submitted drug product is identical to the drug product approved on the NOC and to the drug product studied in the bioavailability studies.

- **Third Party Authorization -** Where a third party is involved with a submission, a letter should be submitted from the NOC holder confirming the business arrangement between the submitting party and the NOC holder. Manufacturers must also identify if the third party has information on file with Health Canada on New Drug Submission or Abbreviated New Drug Submissions For Subsequent Market-Entry (NDS/ANDS). Depending on the nature of the relationship, the letter from the NOC holder must provide an authorization to the third party to assume responsibility for the submission or authorization to submit the product on the NOC holder's behalf.

- **Consent Letters -** All parties which may have information on file with Health Canada, PMPRB, and other provinces relating to the product must provide a consent letter allowing communication with these bodies as outlined in 12.(1)(b). If the submission makes reference to another company's drug product, then the consent letter should be provided by both companies, one making the submission as well as the company of the drug product which is referred to.

- **Proposed Drug Benefit Price -** The NOC holder or the third party which holds the rights to sell the submitted product in Canada must provide the proposed Drug Benefit Price as outlined in 12.(1)(d).

- **Ability to Supply.** The NOC holder or the third party which holds the rights to sell the submitted product in Canada must also provide the confirmation of ability to supply the product as outlined in 12.(1)(e).

12.(1)(a) evidence that Health Canada has approved the product for sale in Canada, a copy of the product's drug notification form issued by Health Canada and, subject to subsection (2), a copy of the product monograph approved by Health Canada;

Interpretation

The Ministry requires evidence that Health Canada has considered the efficacy, safety and quality of a drug product and has approved it for sale in Canada. The following documents will be accepted as evidence of approval by Health Canada:

- Notice of Compliance (NOC); **and**
- Drug Notification Form (DNF); **and**
- product monograph.

Points of Clarification

Notice of Compliance and Drug Notification Form

The Ministry will accept a copy of the product's most recent NOC and DNF. When a drug product was approved without a NOC (i.e., "old" drugs), the Ministry will require a copy of Health Canada's DNF. The DNF should be completed, dated and signed by a senior company official.

Note: The DNF is also known as the drug identification number (DIN) form.

Product Monograph

The product monograph should contain the date of Health Canada's approval and the company name and product name that corresponds to the NOC.

If Health Canada did not approve a product monograph (e.g., "old" drugs), the manufacturer should submit the information generally included in the product monograph. Please refer to the **Drugs Directorate Guideline: Product Monograph** and subsection 12.(2) of these guidelines for more detail.

12.(1)(b) a letter authorizing the Minister to gain access to all information with respect to the product in the possession of Health Canada the Patented Medicine Prices Review Board established under section 91 of the *Patent Act* (Canada) or of the government of any province or territory in Canada and authorizing the Minister to disclose any information with respect to the product in the possession of the Ministry to Health Canada, the Patented Medicine Prices Review Board or to the government of a province or territory in Canada;

Interpretation

As federal and provincial governments work to harmonize their drug review process, it is important for the Ministry to be able to communicate freely with other regulatory agencies. Manufacturers can satisfy this requirement by providing the Ministry permission, in writing, to access all product information filed with Health Canada, other regulatory agencies (i.e., provinces/territories) and with the Patented Medicine Prices Review Board (PMPRB). Letters should be:

- from the holder of the NOC; and
- dated and signed by a senior company official; and
- free of any restrictive clauses.

Points of Clarification

Only letters **free of any restrictions** will be accepted. The letter should authorize the Ministry to access any information pertaining to the drug product at any time. In the past, manufacturers included restrictions or limitations, such as requiring the notification of the manufacturer before obtaining information from Health Canada, and/or having a representative of the manufacturer present when the Ministry obtains information. A letter with any restrictions will not satisfy this requirement, and the submission will be deemed incomplete.

When a third party is involved in filing a submission, a letter is required from all of the parties which may have information regarding the product on file with Health Canada – i.e., NOC holder, manufacturer, distributor, etc.

To assist manufacturers, the Ministry has developed a template letter which is included on the next page; copies are also available in Part VI and on the Ministry's website. If manufacturers choose to use the template, they should ensure that it is printed on company letterhead, dated and signed by an appropriate senior company official.

Template Letter of Consent
Allowing Communication with Health Canada, Provinces and Territories, and PMPRB

[Manufacturer's letterhead]

[Date]

Director
Drug Programs Branch
Ministry of Health and Long-Term Care
3rd Floor, 5700 Yonge Street
Toronto, ON M2M 4K5

Dear Director:

REFERENCE: *[Product name/generic name, strength, and dosage form]*

This letter authorizes the Ontario Ministry of Health and Long-Term Care to gain access to all information with respect to the product in the possession of Health Canada or of the government of any province or territory in Canada or the Patented Medicine Prices Review Board (PMPRB). Furthermore, this letter authorizes the Minister to disclose any information with respect to the product in the possession of the Ministry to Health Canada or to the government of a province or territory in Canada or the PMPRB.

[Signature]

[Name and Title of Senior Company Official]

12.(1)(d) the proposed drug benefit price of the product;

Interpretation

The manufacturer should state clearly the proposed Drug Benefit Price (DBP) for each product. The DBP should include, where applicable:

- price per smallest unit (e.g., tablet, capsule, gm or mL, etc.); and
- price per smallest dispensable unit (e.g., kit, ampoule, prefilled syringe, vial combination package, etc.).
- for listing purposes, the DBP must be expressed to four decimal places ($0.0000).

12.(1)(e)	evidence that the manufacturer is able to supply the product at the proposed drug benefit price in a quantity sufficient to meet the anticipated demand for the product;

Interpretation

The manufacturer must be able to supply the drug product at the submitted price in a quantity sufficient to meet the anticipated demand. To satisfy this requirement, the manufacturer **must** submit a confirmation letter. The letter should:

- include confirmation of the ability to supply product at the submitted price (i.e., proposed Drug Benefit Price) for distribution in a quantity sufficient to meet the anticipated demand; and

- be free of any conditions.

Points of Clarification

The Ministry does not allow conditional price increases.

To assist manufacturers, the Ministry has developed a template letter which is included on the next page; copies are also available in Part VI and on the Ministry's website. If manufacturers choose to use the template, they should ensure that it is printed on company letterhead, dated and signed by an appropriate senior company official.

Template Letter Confirming Ability to Supply Product at Proposed DBP

[Manufacturer's letterhead]

[Date]

Director
Drug Programs Branch
Ministry of Health and Long-Term Care
3rd Floor, 5700 Yonge Street
Toronto, ON M2M 4K5

Dear Director:

REFERENCE: *[Product name, generic name, strength and dosage form]*

This letter is to confirm that *[name of manufacturer]* is currently able to supply the above drug product at the proposed Drug Benefit Price in a quantity sufficient to meet the anticipated demands for this product.

[Signature]

[Name and Title of Senior Company Official]

12.(1)(h) clinical studies and, if available, other clinical evidence of the product's therapeutic effectiveness or efficacy and of the product's safety, including any information that relates to adverse drug reactions and any existing clinical studies comparing the product's therapeutic effectiveness or efficacy and the product's safety to that of other products or treatments; and

Interpretation

Manufacturers may satisfy this requirement by submitting:

- a completed Clinical Data Checklist; and
- clinical evidence, including:
- the Comprehensive Summary or equivalent documentation accepted by Health Canada (as described in Health Canada's New Drug Submission Guideline); and
- a summary of the critical studies; and
- any additional studies completed after the New Drug Submission (NDS) was filed; and
- complete bibliography of published and unpublished studies.

The submission will be deemed incomplete if any of the above are missing without an adequate explanation.

Points of Clarification

Clinical Data Checklist

The Clinical Data Checklist was developed based on the guidelines that DQTC reviewers use during their evaluation. It was designed to help manufacturers prepare submissions that are easy to review and ensure submissions proactively address the DQTC's usual questions.

For each question on the Clinical Data Checklist, manufacturers should provide short answers below the question and direct reviewers to the supporting reference page(s). If a question on the Clinical Data Checklist does not apply, please indicate not applicable (N/A) on the checklist and provide a rationale if necessary. A copy of the Clinical Data Checklist is included at the end of this subsection; copies are also available in Part VI and on the Ministry's website.

Clinical Evidence

In evaluating therapeutic effectiveness and safety, the Ministry and the DQTC place greater reliance on well-designed, comparative clinical trials than on other sources of data. Of the data submitted to Health Canada, manufacturers should submit the Comprehensive Summary relating to the clinical studies of interest. Studies mentioned in the Comprehensive Summary should be cross-referenced to the full study reports and/or manuscripts within the Formulary/CDI submission. Information on Phase 1 studies should be omitted and letters from opinion leaders are rarely helpful.

It is suggested that the clinical data be organized in the following fashion: critical studies and summary (published and unpublished studies that address the key clinical issues); other studies; and supporting documents (e.g. abstracts, consensus statements, review articles, and opinion papers).

Submitted vs. Clinical Study Drug Product

The formulation marketed in Canada should be bioequivalent to those used by the investigators in the clinical studies. In cases where the drug product used in the clinical studies is different from the submitted product, (e.g., different product name, different manufacturing source or manufacturer name etc.) evidence is required to demonstrate the linkage between the product referred to in the master formulation and to the product submitted for listing.

A letter confirming that the two formulations and manufacturing processes are identical except for embossing and labelling may be satisfactory. The letter should be dated and signed by a senior company official. Should questions arise, it may be necessary to provide further information including the master formulation and documentation regarding the manufacturing and quality control (e.g., production worksheets, Certificates of Analysis).

Submissions will be deemed incomplete and will remain as such until the Ministry has been satisfied that the linkage has been sufficiently established between the various products referred to in the submission.

Additional Strengths

When manufacturers submit several strengths of a specific dosage form concurrently, additional strengths of an already-listed drug product, they should refer to subsection 12.(3) of O. Reg. 201/96 under the *Ontario Drug Benefit Act* to determine if the exemption for additional strengths applies. If the exemption does not apply, then they must provide clinical studies for each strength of the drug product.

Additional Formats

When manufacturers submit additional formats of a listed single source product, they should refer to subsection 12.(3.1) of O. Reg. 201/96 under the *Ontario Drug Benefit Act* to determine if the exemption for additional format applies. If the exemption does not apply, then they must provide clinical studies for each format of the drug product.

Extended Release Drug Products

Extended release products will be considered when:

(a) Clinical studies in relevant patient populations have demonstrated the safety and efficacy of the active ingredient when administered as the extended release product; and

(b) The extended release dosage form possesses demonstrated therapeutic advantages in treating the disease for which the product is indicated.

Therapeutic advantage is defined as:

- improved efficacy relative to the conventional dosage form with no increase in toxicity, or
- less toxicity with improved or similar efficacy.

(c) If the product does not meet criterion (b), then listing may be considered if:

- a demonstrated improvement in compliance results in an increase in clinical effectiveness; or
- suitable conventional dosage form(s) already listed are more expensive; or
- suitable conventional dosage form(s) of the drug are not listed and/or readily available.

Combination Products

Combination products will be considered if:

a) each component of the combination makes a contribution to the claimed effect; and

b) there is a pharmacological and pharmaceutical rationale for the mixture; the effect of each component should extend throughout the recommended dosage interval of the combination; and

c) the dosage of each component (amount, frequency, duration) is such that the combination is safe and effective for a significant proportion of the patient population requiring the therapy, as defined in the drug labelling; and

d) the cost is comparable to, or less than that of, similar medications prescribed as one or more single entities; or

e) a demonstrated improvement in compliance results in an increase in clinical effectiveness.

Formatting and Organizing Clinical Data

In order to better guide manufacturers, the following are offered as suggestions to facilitate the DQTC review of clinical data submitted:

1. The Ministry and the DQTC will balance the therapeutic efficacy, safety and cost-effectiveness of a product with that of suitable alternative agents, where appropriate. Ideally, multiple comparators should be evaluated. A good strategy would be to provide a comparison with the least expensive and the most widely used alternatives. Manufacturers should bear in mind that while one alternative may be a listed benefit, others may be reimbursed though the Individual Clinical Review (Section 8) mechanism. A higher-priced alternative will be considered for listing if it offers a significant therapeutic advantage. In these instances, a pharmacoeconomic analysis is of critical importance.

2. Any new evidence that was not submitted to Health Canada that may assist the DQTC in drawing a comparison between the new drug and listed or alternative products should be submitted.

3. To assist the Ministry and the DQTC in making decisions pertaining to the ODB population, clinical data in the relevant patient populations (e.g., elderly, women or children) should be submitted.

4. Information on the incidence and descriptions of adverse drug reactions should include data collected from:
   - reports on adverse drug reactions and expected/unexpected side effects; and
   - clinical studies and medical experience; and
   - any post-marketing experience conducted by the manufacturer or obtained from prescribing physicians.

5. Clinical summaries are helpful, but not required. Very brief summaries are rarely helpful.

6. Unpublished data are considered by the DQTC, however, due to the extensive length of some of the study reports, manufacturers are encouraged to prepare unpublished data as they would a publication manuscript.

7. Administrative details (refer to Part II of these guidelines for more details):
   - sturdy binders, not wider than 7.2cm (3 inches), should be used; and
   - each binder should be clearly labelled; and
   - a table of contents should be provided in each binder; and
   - submissions should be duplexed and paginated; and
   - large, labelled tabs should be used.

CLINICAL DATA CHECKLIST

Product Name/Manufacturer: ____________________

Page Ref(s)

Drug Product

1. What is the pharmacological mechanism of the drug? ________
2. What are the drug's Health Canada approved indications? ________
3. What is the recommended dose range and duration of therapy? (Please include relevant patient populations - e.g., the elderly) ________
4. What Formulary/CDI listing status is proposed by the manufacturer? ________

Clinical Evidence

1. What are the conclusions of randomized controlled trials supporting the efficacy (i.e. when used under optimal circumstances) of the product? Are trials published in peer-reviewed journals? ________
2. What are the key comparators for this drug product? Which ones are listed in the Formulary/CDI? ________
3. What are the results of randomized trials comparing the product to listed alternatives on the Formulary/CDI? Are there randomized trials comparing the product to the least costly and most widely used alternative products listed in the Formulary/CDI? ________
4. What are the conclusions of randomized controlled trials supporting the effectiveness (i.e., when used under usual, real world circumstances) of the product? Are trials published in peer-reviewed journals? ________
5. Do the randomized trials use the most clinically relevant outcome measures, or do they use the surrogate outcomes requiring extrapolation to the relevant outcome? Are the end-point(s) sufficiently justified? ________
6. Were any clinical studies conducted in the elderly, women and children? If not, why not? ________
7. Were any of the clinical trials conducted in Canada? ________

Page Ref(s)

8. Are there ongoing trials that would provide additional information on the product?

9. What are the contraindications for the product?

10. What are the side effects of the drug product?

11. Are there particular safety issues of concern to recipients of the ODB program (e.g., safety in the elderly, women and children)?

12. If the product contains a combination of drugs, is there a pharmacologic and pharmacokinetic rationale for the combination? Specifically, does each component of the combination make a contribution to the claimed effect(s)? Is the dose of each component appropriate for the elderly and/or children? Is the effect of either component modified (synergistically or antagonistically) by the addition of the other component?

Drug Utilization

1. What are the Health Canada approved patient population group(s) for the drug?

2. Will clinicians be able to easily and precisely determine which patients should be treated with this drug? Please explain.

3. Are there other clinical uses or trials for non-approved Health Canada indications?

4. Is it likely that clinicians will expand the use of the product for conditions not approved by Health Canada? If not, what is the evidence to support this position?

5. What is the projected number of patients in Ontario covered by ODB who will use the product in a year?

6. Are there utilization data for the drug product in other jurisdictions? If so, please discuss the possible utilization impact for ODB.

12.(1)(i)	evidence demonstrating the benefit of the product in relation to the cost of the product and to any alternative products or treatments.

Interpretation

Manufacturers may satisfy this requirement by submitting:

- completed Pharmacoeconomic Analysis Summary; and
- completed Pharmacoeconomic Worksheet and study, if applicable; and
- ODB Financial Impact Analysis Summary.

Points of Clarification

Pharmacoeconomic Analyses

The Ministry and the DQTC are interested in evaluating the value-for-money of new drug product(s), particularly in comparison to alternatives already listed in the ODB Formulary/Comparative Drug Index. Pharmacoeconomic analyses provide the DQTC with an evidence-based opportunity to assess if there are any additional cost considerations that should be taken into account other than the cost of the medication alone.

For full instructions on preparing a pharmacoeconomic analysis, please refer to the Ministry's publication, **Ontario Guidelines for Economic Analysis of Pharmaceutical Products**, available on the Ministry's website. Only submissions prepared according to the Ontario guidelines will be accepted. Any other format will be accepted only in exceptional circumstances and may delay review of the submission.

While not all submissions to the Ministry require a full cost-effectiveness analysis, some form of economic evaluation and summary is necessary for all products. A starting point would be a tabulation of costs of therapy associated with the submitted product and appropriate comparator(s) and an itemization of the important respective outcomes.

When drugs are equally effective and have similar side effect profiles, a comparison of total costs of therapy alone (i.e., a cost minimization analysis) may be appropriate. In the situation where the new product actually improves outcomes at a lower cost (i.e., dominant therapy), then a cost minimization analysis is also sufficient. If the new product has an incremental cost (drug price and/or total therapy cost) with an incremental gain in efficacy or other outcomes, then a cost effectiveness, utility or benefit analysis would be indicated. Cost utility analyses should be conducted especially when the value of the therapy seems to relate to improvements in quality-of-life. Cost impacts outside of drug expenditures are very important in the evaluation of pharmaceutical products. These costs should be itemized carefully and realistic unit costs should be assigned from any of a number of standard resource references (e.g. case costing systems in hospitals, schedule of benefits for physicians and laboratories).

Pharmacoeconomic Analysis Summary

Although not all drug products require a full detailed analysis, the manufacturer must address the pharmacoeconomic profile of each drug product. In the Pharmacoeconomic Analysis Summary, the manufacturer should indicate whether a detailed economic analysis has been included or justify its absence. Manufacturers must submit a summary for each strength and dosage form of the drug product.

In the Pharmacoeconomic Analysis Summary, the costs of therapy associated with the submitted product and appropriate comparators(s) should be tabulated and the important respective outcomes should be quantified. These are laid out in Sections I, II and III of the sample Pharmacoeconomic Analysis Summary that follows at the end of this subsection; copies are also available in Part VI and on the Ministry's website.

The cost of therapy should clearly state the drug, dose, duration, daily cost and cost per usual course. Note that the regimen used for costing should reflect the doses and duration used in clinical trials supporting the efficacy of the product. The cost of comparative therapies should follow a similar process. It should also be stated if dosing regimens of products in current clinical use differ from the literature (e.g., current clinical practice may be to dose a product twice daily whereas older studies dosed the product three times daily). Comparative therapies may include the lowest cost alternative, most commonly used products based on utilization data, or products recommended in published guidelines. Products other than those listed in the Formulary/CDI may be included as comparators of interest.

A concise summary of the relevant comparative clinical outcomes, both measured in clinical trials and extrapolated from models (e.g., success rate, adverse events, deaths, projected survival), is vital to judge the value of the therapy and to clearly provide guidance for further economic evaluation.

Pharmacoeconomic Analysis Work Sheet

Submissions that include a pharmacoeconomic analysis must also have a completed Pharmacoeconomic Analysis Work Sheet. For each question, the manufacturer should provide a concise answer (bullet points are adequate) and direct reviewers to reference pages or tables within the body of the economic report or in the supporting literature for clarification. A sample Pharmacoeconomic Analysis Work Sheet is included at the end of this subsection; copies are also available in Part VI and on the Ministry's website.

ODB Financial Impact Analysis Summary

A financial impact analysis provides both the Ministry and the DQTC the opportunity to understand the impact of a new drug product on Ministry expenditures. The DQTC considers the analysis in conjunction with the pharmacoeconomic data in assessing the incremental and overall cost considerations of a new product. This forecast is also utilized by the Ministry when a positive recommendation has been received from the DQTC, in developing ODB expenditure forecasts and assessing written agreements. A forecast for three consecutive twelve-month periods must be submitted.

In assessing the financial impact, the Ministry is interested in the yearly expenditures (drug costs only) for the product(s) under consideration. Drug costs should exclude up-charge and professional fee. The expenditures should be projected for three consecutive twelve-month periods irrespective of the anticipated date of Formulary/CDI listing. Forecasts should be provided for each individual drug product (e.g., strength and dosage form). In the event that not all drug products submitted are recommended for Formulary/CDI listing, it is useful to have a breakdown of projected expenditures by individual drug product. References should be cited where applicable.

The assumptions underlying the forecast should include:

- summary of potential market size, rate of growth, and extrinsic factors that may affect market size; and
- initial market capture and how entry impacts existing Formulary/CDI product utilization (including the rate of growth/decline of other comparators); and
- estimate of the average claim cost and number of claims underlying forecast; and
- anticipated changes, including generic entry or the entry of new competitor drugs, that may affect market share projections.

The manufacturer should also describe changes in the rate of uptake of the product, projected growth targets, as well as growth in the overall market expected. In addition, the manufacturer should describe the net effect on other Formulary/CDI alternatives.

To assist manufacturers, an ODB Financial Impact Analysis Summary has been developed; it may be helpful to manufacturers in understanding the factors considered by the Ministry in developing expenditure forecasts. A copy of the ODB Financial Impact Analysis Summary is included at the end of this subsection; copies are also available in Part VI and on the Ministry's website.

Although an ODB financial impact is required, the ODB Financial Impact Analysis Summary is optional. Manufacturers are free to make use of their own template. However, use of the template provided will facilitate the Ministry's review of submitted forecasts. It is understood that not all of the information in these templates will be available and/or relevant for every product. Where information is not applicable or not available, it should simply be noted as such.

Note: The manufacturer must notify the Ministry immediately if the price of the submitted drug product changes during the review process, and resubmit any other component of the submission affected by the proposed price change (i.e., estimate of market penetration or pharmacoeconomic data). **Any changes to the submitted price may affect the Ministry's assessment of the drug product.**

PHARMACOECONOMIC ANALYSIS SUMMARY

SECTION I. DRUG PRODUCT

Product Information	
Brand Name / Manufacturer	*Drug X Tablet USP (ACME Ltd.)*
Generic Name / Strength / Dosage Form	*Generic C 5 mg Tablet*
DIN	*01234567*
Usual Dose Regimen/Duration	*5 mg bid x 10 days*
Submitted Price Per Unit	*$2.00 per tab*
Daily Cost *	*$ 4.00 per day*

* based on usual dosing regimen and submitted price, as stated above

Available Package Size (A)	Price (B)	Calculated Price/Unit (C = B/A)	Cost of Usual Dosing Regimen
50	*$ 100.00*	*$ 2.00 per tablet*	*$ 40.00*
100	*$200.00*	*$ 2.00 per tablet*	*$ 40.00*
500	*$ 1000.00*	*$ 2.00 per tablet*	*$ 40.00*

SECTION II. COMPARATOR DRUG PRODUCT / TREATMENT

Please indicate all appropriate drug comparators (including strength and dosage form) and/or treatment comparators for this product.

Generic Name (Mfr) / Strength / Dosage Form	Price *	Equivalent Dosing Regimen for Comparator	Daily Cost	Cost of Usual Dosing Regimen
Generic A (Brand Y Inc) 5 mg USP tab	*$1.00*	*5 mg bid x 10 days*	*$2.00*	*$20.00*
Generic B (Brand Z Inc) 5 mg BP cap	*$1.50*	*5 mg tid x 7 days*	*$4.50*	*$31.50*

* indicate source if other than the price in the Formulary/CDI.

SECTION III. COMPARATIVE OUTCOMES

Drug	Outcome 1 (e.g. successes)	Outcome 2 (e.g. adverse events)	Outcome 3 (e.g. deaths)	Outcome 4 (e.g. projected survival)
Drug X	***$ 70%***	***5%***	***1%***	***20 years***
Generic A	*$ 80%*	*10%*	*2%*	*18 years*
Generic B	*$ 70%*	*10%*	*3%*	*16 years*

References:

Note:

- Appropriate comparators should be listed for each strength and dosage form.
- The manufacturer should indicate comparable dosing regimens, including the duration of therapy.
- Where there are multiple source alternatives for the products, the lowest cost interchangeable alternatives should be listed first.
- Where there are listed single source alternatives for the product, these may also be listed.
- Where there are no appropriate listed single or multiple source alternatives, other marketed drug products may be listed.
- Where the appropriate comparison is not a drug but another treatment, please attach a separate sheet outlining the treatment and indicating why it is the appropriate comparator.

SECTION IV. PHARMACOECONOMIC ANALYSIS

Pharmacoeconomic Analysis included? [X] Yes [ ] No

Pharmacoeconomic Worksheet included? [X] Yes [ ] No

If yes, please indicate type of analysis:
[ ] Cost-Minimization
[ ] Cost-Consequence
[X] Cost-Effectiveness
[ ] Cost-Utility
[ ] Cost-Benefit

If a detailed economic analysis is **not** included, please outline the reasons below:

PHARMACOECONOMIC ANALYSIS WORK SHEET

Product Information	
Drug Product (generic name/strength/dosage form)	*Drug X Tablet USP* *Generic C 5 mg Tablet*
Name of Manufacturer	*ACME Ltd.*

Please complete each of the following questions:

1. (a) What is the question being asked in the analysis?
   (b) What type of economic analysis was performed to answer the question?
      i Cost comparison
      ii. Cost-consequence analysis
      iii. Cost-effectiveness analysis
      iv. Cost-utility analysis
      v. Cost-benefit analysis
   (c) What is the justification for the approach taken?

2. (a) Did the study involve a comparison of alternative treatments for patients with the same clinical condition?
   (b) Are those alternatives explicitly stated?
   (c) Is the analysis therefore an incremental analysis?

3. (a) Is the viewpoint or perspective for the analysis stated clearly?
   (b) Is it a societal perspective, third-party payer perspective, patient perspective?
   (c) Is the analysis presented in a disaggregated fashion showing these perspectives separately?

4. (a) Was the evidence of the product's efficacy established through randomized trials?
   (b) Was this evidence of efficacy supplemented by evidence of effectiveness applicable to the patients covered by the Ontario Drug Benefit program?
   (c) Was the latter evidence derived from studies documenting routine use in clinical practice?

5. (a) Are the methods and analysis displayed in a clear and transparent manner?
   (b) Are the components of the numerator (cost of each alternative) and denominator (clinical outcomes of each alternative) displayed?
   (c) Are clinical outcomes expressed first in natural units and then translated into alternative units such as benefits or utility? (See Section 3.4.d. of the *Ontario Guidelines for Economic Analysis of Pharmaceutical Products* for suggested format).

6. Are all important and relevant costs and consequences (outcomes), including adverse effects, for each alternative identified?

7. (a) Are costs and consequences modelled as in a decision tree with information derived from a variety of sources; OR
   (b) estimated directly from a variety of sources; OR
   (c) estimated directly from a specific patient population?

8. (a) Are capital costs and overhead costs included as well as operating costs?
   (b) How were they measured?

9. How were indirect costs identified and estimated?

10. How was quality of life measured?

11. (a) What equity assumptions were made in the analysis?
    (b) For example, are QALYs gained by any individual considered equal?

12. (a) If some variables were difficult to measure, how did the authors handle this difficulty?
    (b) Did they slant the analysis all in favour of one intervention in order to bias the analysis against the desired result?

13. (a) Were extensive sensitivity analyses performed?
    (b) What were the ranges of values for variables in the sensitivity analyses?

14. (a) Is quality of life an important component of an economic analysis of this question?
    (b) How sensitive is the estimate of cost utility to variations in quality of life?

15. (a) Is there an estimate of the aggregate incremental expenditure required for the province to provide this product to patients covered by its programs?
    (b) What is the estimate of aggregate incremental costs?
    (c) Does this estimate cover all of the major indications for use of the product?

16. (a) Has the incremental cost-effectiveness ratio been estimated for a special clinical indication that represents the majority or all of its expected use by those covered under the Ontario Drug Benefit program?
    (b) Do these other indications involve a large amount of utilization for which the ratio may be very different?

17. (a) Who performed the analysis?

    (b) Did the authors of the report sign a letter indicating their agreement with the entire document presented?

    (c) Does the report indicate that the authors had independent control over the methods and right to publish the analysis regardless of its results?

18. What is the "bottom line" result of the analysis in quantitative terms? The answer to this question will be statements like the following:

    - The cost per QALYs gained for using this product compared to the alternative is \$X, or ranges from \$Y to \$Z.
    - The use of this product compared to the stated alternative will result in an expected incremental expenditure of \$X per patient treated with a net reduction of Y major adverse clinical events (e.g., cardiac deaths) and Z minor clinical events (e.g., side effects).

ODB FINANCIAL IMPACT ANALYSIS SUMMARY

SECTION I. DRUG PRODUCT

Product Information	
Drug Name / Manufacturer	
Generic Name / Strength / Dosage Form	
Proposed reimbursement status	
DIN	
Submitted Price Per Unit	
Daily Cost *	
Usual Dosing Regimen/Duration	
Maximum Dosing Regimen/Duration	

* based on usual dosing regimen and submitted price, as stated above.

SECTION II. SUMMARY OF ODB FINANCIAL IMPACT

Summary Item	Manufacturer's Submitted Estimates		
	Year 1	Year 2	Year 3
Drug Cost* ($)			
Claims			
Net Expenditure/(Savings)			

* Drug Cost should exclude up-charge and professional fee.

SECTION III: UNDERLYING ASSUMPTIONS FOR KEY FACTORS IN FORECAST – MOST LIKELY SCENARIO

For each parameter, it would be helpful to organize the data according to Baseline (where applicable), Year 1, Year 2, and Year 3 with the confidence level (high, medium or low) and the evidence/data sources.

Parameter	Baseline	Year 1	Year 2	Year 3	Confidence Level (high/med/low)	Evidence used to support assumptions
1. **Disease Demographics**						
(e.g. number of patients with the disease, number of patients consulting physicians, number of patients diagnosed, number of patients treated, number of ODB recipients)						
2. **Market Share** For (1) submitted product; (2) comparators within therapeutic class; (3) other relevant comparators for therapeutic indication.						
a) Patients (e.g. new patients, patients switching from competitor products)						
b) Claims (e.g. claims/ patient, claims/year)						
3. **Growth Rate** (e.g., compliance rate, withdrawal rate, potential impact of future listings such as new generic products)						
4. **ODB Expenditures** For (1) submitted product; (2) comparators within therapeutic class; (3) other relevant comparators for therapeutic indication.						
a) Cost per claim (e.g. doses per day, cost per dose, cost per day)						
b) ODB claims per year						
c) Total expenditures						
d) Net impact						

SECTION IV. CONTINGENCY ESTIMATES – PESSIMISTIC AND OPTIMISTIC SCENARIOS

For each parameter, it would be helpful to organize the data according to Baseline (where applicable), Year 1, Year 2, and Year 3 with the confidence level (high, medium or low) and the evidence/data sources.

Parameter	Baseline	Year 1	Year 2	Year 3	Confidence Level (high/med/low)	Evidence used to support assumptions
PESSIMISTIC SCENARIO (SUBMITTED PRODUCT PERFORMANCE IS BELOW EXPECTATIONS)						
Total annual ODB expenditure (submitted product) ($)						
Incremental change vs. most likely forecast ($)						
Total ODB expenditure (therapeutic class) ($)						
Incremental change vs. most likely forecast ($)						
Rationale for changes (list/identify any significant modifications in assumptions)						
OPTIMISTIC SCENARIO (SUBMITTED PRODUCT PERFORMANCE EXCEEDS EXPECTATIONS)						
Total annual ODB expenditure (submitted product) ($)						
Incremental change vs. most likely forecast ($)						
Total ODB expenditure therapeutic class) ($)						
Incremental change vs. most likely forecast ($)						
Rationale for changes (list/identify any significant modifications in assumptions)						

12.(2) If Health Canada has not approved a product monograph for a drug product, the manufacturer of the product may, instead of submitting a copy of the product monograph as required under clause (1)(a), submit to the Minister the following information:

1. Pharmaceutical information.
2. Information with respect to the product's clinical pharmacology.
3. Information as to the product's indications and clinical use.
4. A list of any contraindications, warnings or precautions in the use of the product and of possible adverse reactions to its use.
5. A list of symptoms of an overdose of the product and information as to the treatment of an overdose.
6. Information with respect to the dosage and administration of the product.
7. Information regarding the availability of dosage forms for each strength of the product marketed in Canada.

Interpretation

When a drug product was approved by the Health Canada without an official product monograph (i.e., 'old' drugs), the Ministry will accept information generally included in the official product monograph (listed above) in its place. A manufacturer may submit a revised product monograph to satisfy this regulation.

Please refer to the **Drugs Directorate Guideline: Product Monograph** for more detail.

12.(3) A manufacturer may satisfy the condition set out in clause (1)(h) for a strength of a drug product by submitting the clinical evidence referred to in clause (1)(h) for another strength of the same dosage form of the drug product, if the evidence is sufficient for the purposes of evaluating the therapeutic effectiveness or efficacy and the safety of both the strengths of the dosage form of the product.

Interpretation

Manufacturers who wish to use this exemption should provide:

- evidence of proportionality and bioequivalence (if not proportional); and
- justification for the additional strength.

This exemption allows for the submission of clinical data for one strength to be applied to other strengths of the same dosage form of a drug product. When a drug does not qualify for this exemption, manufacturers must provide separate clinical studies for each strength of the drug product.

Points of Clarification

Evidence of Proportionality in Composition or Bioequivalence

If the different drug strengths have proportional formulations or have the same ingredients with only modest changes in the quantities of inactive ingredients, a manufacturer may rely on the same clinical data for two strengths of the drug product. Manufacturers should provide evidence that the different strengths have the same proportions (i.e., master formulation should be provided for all the strengths).

If the additional strength of the product is not proportional in composition and major formulation differences exist between the strengths, the manufacturer must submit a comparative bioavailability study demonstrating that the two strengths are bioequivalent in order to rely on the clinical data of another strength of product.

Please refer to the interpretation of subsection 6.(1)(h) of Regulation 935 under the *Drug Interchangeability and Dispensing Fee Act* for more detail on the data required to demonstrate bioequivalence. The reference product used in the bioequivalence study must be the product studied in the clinical trials.

Justification for an Additional Strength

Manufacturers must provide a justification for the additional strength and describe the patient population that is most likely to make use of this additional strength. Although not required with this exemption, it is helpful to have some data with the additional strength product in the targeted patient population. The manufacturer should also estimate the proportion of patients that the additional strength product would be used for. Although there is an exemption for clinical data for additional strengths of products, there is no exemption for economic data. Manufacturers are still required to describe the economic value and impact of an additional strength as outlined in 12.(1)(i).

A manufacturer making a submission for an additional strength of a drug product already listed in the Formulary/CDI must still submit copies of the clinical studies for the listed strength of the drug product.

Note: Since the master formulation is no longer required for a single source product under O. Reg. 201/96 - Section 12 (ODBA), a manufacturer relying on the proportionality or bioequivalence of an additional strength for an exemption should provide the master formulation for all strengths, including the currently listed drug product. Failure to do so will delay the review process, as the Ministry will have to request the formulation from Health Canada. Please see 6(1)(c) of Regulation 935 under DIDFA for more information on master formulations.

12.(3.1) A manufacturer may satisfy the condition set out in clause (1)(h) for a format of a drug product by submitting the clinical evidence referred to in clause (1)(h) for another format of the drug product, if the evidence is sufficient for the purposes of evaluating the therapeutic effectiveness or efficacy and the safety of both the formats of the product.

Interpretation

Manufacturers who wish to use this exemption should provide:

- evidence of Health Canada's approval of the new format; and
- evidence of bioequivalence; and
- justification for the additional format.

This exemption allows for the submission of clinical data from the listed format to be applied to new formats of a drug product. When a drug does not qualify for this exemption, manufacturers must provide separate clinical studies for each format of the drug product.

Points of Clarification

Where a manufacturer wishes to have an additional format of a listed single source product added to the Formulary/CDI, it may be possible to apply the clinical data from the listed drug product to the new format. It will be necessary to establish a clear linkage between the two drug products. Although the Ministry will be guided by the requirements imposed by Health Canada for the new format, additional clinical evidence may be required to demonstrate that the clinical data for the listed product can be relied upon for the new format. As this is a new exemption, manufacturers are encouraged to clearly outline the evidence upon which Health Canada approved the new format.

Previously, new formats of listed products were not reviewed unless product specific clinical data was available. Such submissions were deemed incomplete unless clinical data were made available. This new exemption allows for submissions for new formats of listed products, without product specific clinical data, to be deemed complete and to be reviewed by the DQTC. During the course of their review, the DQTC may recommend that clinical data is required in order to evaluate whether the new format is suitable for reimbursement. It is likely that, if Health Canada required product specific clinical data before approving the new format, the DQTC would require the same information. In these instances, manufacturers are encouraged to provide the clinical evidence. Generally, where a new format is likely to be used in a specific patient population, data in that population is helpful.

As well, if the new format is likely to incur additional costs to the program, evidence to justify the additional cost will generally be required.

The tables on the following page provide a guide as to the data that may be required for new formats.

Evidence of Health Canada's Approval of the New Format

The Ministry requires evidence that Health Canada has considered the efficacy, safety and quality of the new format and has approved it for sale in Canada.

Evidence of Bioequivalence

For new formats of oral dosage forms, a manufacturer may rely on the same clinical data for the original format of the drug product. Manufacturers must submit a comparative bioavailability study demonstrating that the two formats are bioequivalent in order to rely on the clinical data of another format.

Please refer to the interpretation of subsection 6.(1)(h) of O. Regulation 935 under the *Drug Interchangeability and Dispensing Fee Act* for more detail on the data required to demonstrate bioequivalence. The reference product used in the bioequivalence study must be the product studied in the clinical trials.

Justification for the Additional Format

Manufacturers must provide a justification for the new format and describe the patient population that is most likely to make use of the new format. Although not required with this exemption, it is helpful to have some data with the new format in the targeted patient population. The manufacturer should also estimate the proportion of patients that the new format would be used for. Although there is an exemption for clinical data for new formats, there is no exemption for economic evidence. Manufacturers are still required to describe the economic value and impact of an additional strength as outlined in 12.(1)(i).

A manufacturer making a submission for an additional format of a drug product already listed in the Formulary/CDI must still submit copies of the clinical studies for the listed strength of the drug product. This will avoid delay in retrieving archived information and speed the review process.

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Tables of New Format Information

Injectable dosage form: Line extensions may include a new formulation (e.g., dry powder to ready-to-use solution) or a new package format.

Line Extension of a Brand Product	Strength	Dosage Form	Route of Administration	Formulation	Package	Required Clinical Data
New: Multi-dose pen for injection **Original:** Single-dose vial for injection	Same	Same (injection)	Same (IV)	Different	Different	Reference or use of data from listed product.
New: Prefilled Syringe **Original:** Multi-dose vial	Same	Same (injection)	Same (IV)	Different	Different	Reference or use of data from listed product.
New: IV Minibag **Original:** Dry powder vial for injection (after reconstitution)	Same	Same (injection)	Same (IV)	Different	Different	Reference or use of data from listed product.
New: Multi-dose vial **Original:** Dry powder vial for reconstitution	Same	Same (injection)	Same (IV)	Different	Different	Reference or use of data from listed product.

Solid oral dosage form: Line extensions may include a new formulation (e.g., tablet versus capsule) or a new package format.

Line extension of a brand product	Strength	Dosage Form	Route of Administration	Formulation	Package	Required Clinical Data
New: tablet **Original:** capsule	Same	Different	Same (oral)	Different	N/A	Reference or use of data from listed product. **Biostudy required.**
New: sachet or sprinkle capsules **Original:** tablet	Same	Different	Same (oral)	Different	Different	Reference or use of data from listed product. **Biostudy required.**

Oral liquids: Line extensions may include a change in formulation (e.g., oral liquid versus tablet) or a new package format.

Line extension of a brand product	Strength	Dosage Form	Route of Administration	Formulation	Package	Required Clinical Data
New: oral liquid **Original:** tablet	Different	Different	Same (oral)	Different	Different	Reference or use of data from listed product. **Biostudy required.**

12.(4)	A manufacturer may satisfy the condition set out in clause (1)(h) for a drug product by submitting to the Minister the clinical evidence referred to in clause (1)(h) with respect to another drug product and submitting evidence that satisfies the Minister that the two products are bioequivalent.

12.(5)	Subsection (4) does not apply if the drug product that the manufacturer seeks to have designated is the drug product of a drug for which there exists a listed drug product.

Interpretation

When a manufacturer is seeking a single source listing of a generic drug product, the Ministry will consider:

- the completed Clinical Data Checklist; and
- clinical evidence; and
- evidence of bioequivalence.

This regulation allows manufacturers to list a multiple source product as a single source product under Section 12 of O. Reg. 201/96 of the *Ontario Drug Benefit Act* (ODBA), when another brand of a particular drug is not already listed in the Formulary/CDI. The purpose of this regulation is to allow a manufacturer to make a submission for a generic product under ODBA when there is no listing for that drug.

Subsection (4) does not apply if another strength or dosage form of the drug is already listed in the Formulary/CDI.

When this exemption applies, the manufacturer of the multiple source drug product may be exempt from the clinical requirements specified in subsection 12.(1)(h) but must satisfy all other requirements specified in Section 12.

Points of Clarification

Clinical Data Checklist and Clinical Evidence

A completed Clinical Data Checklist must accompany the clinical trials of the reference product. More information on the Clinical Data Checklist and clinical evidence can be found in the interpretation of subsection 12.(1)(h) of O. Reg. 201/96 under ODBA.

Evidence of Bioequivalence

Manufacturers can demonstrate the submitted product is bioequivalent with the reference product by providing full comparative, product-specific bioequivalence study data. When Health Canada declares a product bioequivalent with the Ministry's original product, the manufacturer may submit the information outlined in subsection 6.(1)(h) under the *Drug Interchangeability and Dispensing Fee Act* (DIDFA) as evidence of interchangeability. For more information, please refer to the interpretation of subsection 6.(1)(h) in Part IIIB of these guidelines.

12.(6) Subsection (1) does not apply to a drug product that is designated as an interchangeable product under the *Drug Interchangeability and Dispensing Fee Act*.

Interpretation

Multiple source products that are submitted, evaluated, and designated interchangeable, according to Section 6 of Regulation 935 under the *Drug Interchangeability and Dispensing Fee Act*, are exempt from the submission requirements in Section 12 of O. Reg. 201/96 under the *Ontario Drug Benefit Act* (ODBA). If a product is designated as interchangeable, it will be listed in the Formulary/CDI under the ODBA.

12.0.1(1) In addition to the conditions referred to in sections 11 and 12, it is a condition for the designation of a strength and dosage form of a drug product on or after June 1, 1998 that the manufacturer of the product and the Minister enter into a written agreement which shall set out the net costs to the Province in the three-year period following the day the product is designated in relation to;

a) the proposed drug product, if listed; or

b) a group of listed drug product set out in the agreement which shall include the proposed drug product, if listed.

12.0.1(2) Subsection (1) does not apply to a drug product that is designated as an interchangeable product under the *Drug Interchangeability and Dispensing Fee Act.*

Interpretation

An amendment to O. Reg. 201/96 under the *Ontario Drug Benefit Act*, effective June 1, 1998, introduced written agreements as a condition of listing for all new single source products recommended for listing in the Formulary/CDI.

The manufacturer of the product(s) must enter into a written agreement with the Ministry, which includes the net forecasted costs (excluding up-charge and professional fee) to the province in the three-year period (three consecutive twelve-month periods) commencing the day the product is listed.

Points of Clarification

The Ministry encourages manufacturers to submit a written agreement at the time a submission is filed. A draft agreement is not mandatory at this stage. A written agreement is required from the manufacturer after a positive recommendation is made, if it has not been provided. The assumptions used in determining the proposed net costs (e.g., target population, duration of therapy, dosage, product replacement, etc.) must accompany your draft written agreement. A revised ODB financial impact analysis template can be used for this purpose. Since the conditions for listing, if any, may be difficult to predict at the time a submission is provided, manufacturers are given an opportunity to finalize the written agreement dollar amounts after DQTC has considered the product(s) and a recommendation is communicated. In developing the Ministry's forecast for a product, the Ministry considers the specific recommendations made by the DQTC and the manufacturers' submitted ODB Financial Impact. A large discrepancy between the originally submitted financial impact and the written agreement figures would require an explanation.

12.1 The following conditions must be met in order for a designated listed drug product to continue to be designated as a listed drug product:

1. The manufacturer of the product shall give the Minister notice of any change made to the product, including a formulation change, and of any change in the ownership of the manufacturer.

2. The product must be authorized for sale under the *Food and Drugs Act* (Canada).

3. The manufacturer of the product must continue to be able to supply the product at the drug benefit price in a quantity that is sufficient to meet the demand for the product.

4. In the case of a strength and dosage form of a drug product that is designated on or after June 1, 1998, the manufacturer of the product must continue to be a party to a written agreement which shall set out the net costs to the Province during subsequent three-year periods in relation to,

    a) the proposed drug product, if listed; or

    b) a group of listed drug products set out in the agreement which shall include the proposed drug product, if listed.

Interpretation

To maintain a product listing, the manufacturer must comply with the conditions listed above.

Points of Clarification

Paragraph 1 of Section 12.1 ensures that the manufacturer notifies the Ministry of significant changes to drug products contained in the Formulary/CDI, and allows the Ministry to introduce changes, as appropriate, to the Formulary/CDI. The Ministry must be notified of changes to DIN, ownership of the manufacturer, significant changes to the product monograph, master formulation where the changes are significant or affect the bioavailability of the drug product.

Manufacturers should clearly **indicate** which products are affected by the change. Manufacturers should not include those products that are currently not listed in the Formulary/CDI for notification of change. The Ministry will only acknowledge those products listed in the Formulary/CDI. The Ministry may return the list to manufacturers to identify the affected products before it proceeds in assessing the change.

Paragraph 2 of Section 12.1 ensures that for a drug to continue to be designated as a listed drug product, the manufacturer of the product must comply with Health Canada's requirements, including having a valid NOC and/or DNF and making the drug product in accordance with the regulations (e.g., drug product is manufactured according to Good Manufacturing Practice standards).

Specific Applications of Paragraph 1 of Section 12.1

Notification of Change

The notification, dated and signed by the Chief Executive Officer or another senior company official, must be filed within 30 days after Health Canada has approved the change. The notification must include:

- identification of the change(s); and
- a brief explanation for the change(s); and
- confirmation that the bioavailability has not been affected; and
- evidence that Health Canada has approved the change (e.g., Notice of Compliance and/or Drug Notification Form and/or Letter of No Objection and/or Product Monograph, where applicable).

Change in DIN or Ownership

For a change in DIN or ownership, the notification should include:

- identification of the change(s); and
- a brief explanation for the change(s); and
- confirmation that the bioavailability has not been affected; and
- evidence that Health Canada has approved the change: (e.g., new NOC and/or Drug Notification Form or Letter of No Objection); and
- old and new DINs for the drug product, clearly identifying the strengths and dosage forms affected by the change.

Changes to the Product Monograph

Significant changes to the product monograph must be brought to the attention of the Ministry. Significant changes include any changes to indications, significant changes to contraindications, adverse effects and warning/precautions. For a change in product monograph or prescribing information, the notification should include:

- identification of the change(s); and
- a brief explanation for the change(s); and
- evidence that Health Canada has approved the change:
  (e.g., new NOC and/or Drug Notification Form or Letter of No Objection); and
- old and new DINs for the drug product, clearly identifying the strengths and dosage forms affected by the change; and
- a copy of the new product monograph.

Changes in the Master Formulation

For significant changes in the master formulation (changes which may affect the bioavailability of the product) the notification should include the old and new formulations and highlighting the differences:

- identification of the change(s); and
- a brief explanation for the change(s); and
- confirmation that the bioavailability has not been affected (for oral formulations); and
- evidence that Health Canada has approved the change:
  (e.g., new NOC and/or Drug Notification Form or Letter of No Objection); and
- old and new DINs for the drug product, clearly identifying the strengths and dosage forms affected by the change (if applicable); and
- product monograph, if applicable.

Change Not Approved by Health Canada

If Health Canada has not approved the change (i.e.,"old" drugs), the manufacturer should submit documentation demonstrating that the bioavailability of the drug product was not affected. For a change in master formulation (including specifications for aqueous solutions), the Ministry will accept:

- identification of the change(s); and
- a brief explanation for the change(s); and
- old and new formulation with the differences highlighted; and
- justification why a bioavailability study is not required, or
- evidence of interchangeability of the old and new formulations.

Changes in Bioavailability

For changes in the bioavailability of a listed drug product, a new bioavailability study (or a justification for not providing a study) is required. Please refer to subsection 6(1)(h) of Regulation 935 under the *Drug Interchangeability and Dispensing Fee Act* for more information on bioavailability evidence.

Note: The lists above are of required information that should be sufficient in the large majority of cases. Should questions arise, the Ministry may request the manufacturer to provide additional information as necessary. Manufacturers may also be required to confirm annually that all the information previously supplied about the drug listed in the Formulary/CDI is accurate and current. If issues or questions arise during the review process, the Ministry may request additional information.

PART III B

INTERPRETIVE GUIDELINES

FOR

DRUG INTERCHANGEABILITY AND DISPENSING FEE ACT

REGULATION 935, SECTION 6

For the vast majority of cases, where Health Canada has declared bioequivalence and the Canadian reference product is identical to the Ontario Ministry's original product, a drug product may be considered for interchangeability designation when the submission meets the following requirements:

6.(1)(a) evidence of Health Canada's approval:

- Notice of Compliance stating the declaration of bioequivalence; and
- Drug Notification Form; and
- product monograph; and

6.(1)(b) consent letter allowing communication with Health Canada and other provinces/territories; and

6.(1)(d) proposed Drug Benefit Price; and

6.(1)(e) letter confirming ability to supply anticipated demand for product at Drug Benefit Price.

Where Health Canada has not declared bioequivalence or the Canadian reference product differs from the Ministry's original product, the submission must also satisfy the following requirements:

6.(1)(c) master formulation; and

6.(1)(h) evidence of interchangeability.

These additional requirements are also needed for Report C product regardless of whether bioequivalence has been declared.

The interpretations for each of these regulations are outlined on the following pages; where necessary, points of clarification and details related to specific applications are also provided. Similar information is provided for regulations 6.(2) through to 6.(7) which deal with various exemptions to the regulations above, and for regulations 7.(2) and 8. which outline the conditions for a product to be designated as interchangeable and to continue to be designated as such. To assist the manufacturer in preparing a submission, various template letters, tables and checklists have been provided; copies of these templates are also available in Part VI and on the Ministry website. (www.gov.on.ca/health).

Note: Over the last few years, several regulations (e.g., 6.(1)(f)) have been revoked and therefore no longer appear in the list above; also, some regulations have been renumbered.

6.(1) It is a condition for each strength and dosage form of a drug product to be designated as interchangeable with other products that the manufacturer of the drug product submit to the Minister,

Interpretation

This section applies to a request to:

- designate a new multiple source product as interchangeable;
- add a new strength of a multiple source product or a new dosage form to the Formulary/CDI; and
- redesignate a multiple source product as an interchangeable product.

Points of Clarification

The Ministry acknowledges all submissions received from manufacturers in writing. Please note that only complete submissions (i.e., those that satisfy all the regulatory requirements) will be considered for listing. The date a submission is deemed complete determines the subsequent ranking of the product versus another in the review process.

Third Party Involvement

The manufacturer named on the Notice of Compliance (NOC) or Drug Notification Form (DNF) who is responsible for the product in Canada can file a submission with the Ministry. It is possible that a party other than the manufacturer named on the NOC/DNF may file a submission. It is also possible that a third party may be involved with a submission in other ways (e.g., product manufacturing). Where the third party assumes the right to distribute and sell a drug, they will be considered to assume responsibility for the product and certain confirmations will be necessary from that third party. Where the third party acts as an agent only, on behalf the NOC holder, all of the confirmatory documentation will be required from the NOC holder.

Under these circumstances, additional documentation will be necessary to clearly establish the relationship of the third party with the holder of the NOC, the relationship between any different drug products referred to in the submission, and to ensure that all requirements are met. The submission will not be deemed complete unless sufficient documentation of all aspects of the submission and the relationships between all parties and drug products are provided and well understood. The listing in the Formulary/CDI will list the name of the manufacturer holding the NOC.

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The requirements related to third party involvement have not been defined by regulation; however, when a third party is involved in a submission, the following documentation should be provided:

- **Product Confirmation Letter -** A letter from the NOC holder dated and signed by a senior company official confirming that the submitted drug product is identical to the drug product approved on the NOC and to the drug product studied in the bioavailability studies.
- **Third Party Authorization -** Where a third party is involved with a submission, a letter should be submitted from the NOC holder confirming the business arrangement between the submitting party and the NOC holder. Manufacturers must also identify if the third party has information on file with Health Canada on New Drug Submission or Abbreviated New Drug Submissions For Subsequent Market-Entry (NDS/ANDS). Depending on the nature of the relationship, the letter from the NOC holder must provide an authorization to the third party to assume responsibility for the submission or authorization to submit the product on the NOC holder's behalf.
- **Consent Letters -** All parties which may have information on file with Health Canada and other provinces relating to the product must provide a consent letter allowing communication with these bodies as outlined in 6.(1)(b). If the submission makes reference to another company's drug product, then the consent letter should be provided by both companies, one making the submission as well as the company of the drug product which is referred to.
- **Proposed Drug Benefit Price -** The NOC holder or the third party which holds the rights to sell the submitted product in Canada must provide the proposed Drug Benefit Price as outlined in 6.(1)(d).
- **Ability to Supply.** The NOC holder or the third party which holds the rights to sell the submitted product in Canada must also provide the confirmation of ability to supply the product as outlined in 6.(1)(e).

6.(1)(a)	evidence that Health Canada has approved the product for sale in Canada, a copy of the product's drug notification form issued by Health Canada and, subject to subsection (2), a copy of the product monograph approved by Health Canada;

Interpretation

The Ministry requires evidence that Health Canada has considered the efficacy, safety and quality of a drug product and has approved it for sale in Canada. The following documents will be accepted as evidence of approval by Health Canada:

- Notice of Compliance (NOC); **and**
- Drug Notification Form (DNF); **and**
- product monograph.

Points of Clarification

Notice of Compliance and Drug Notification Form

The Ministry will accept a copy of the product's most recent NOC and DNF. When a drug product was approved without a NOC (i.e., "old" drugs), the Ministry will request a copy of Health Canada's DNF. The DNF should be completed, dated and signed by a senior company official.

Note: The DNF is also known as the drug identification number (DIN) form.

Product Monograph

The product monograph must contain the date of Health Canada's approval and the company name and product name that corresponds to the NOC.

If Health Canada did not approve a product monograph (e.g., "old" drugs), the manufacturer should submit the information generally included in the product monograph. Please refer to the **Drugs Directorate Guideline: Product Monograph** and subsection 6.(2) for more detail.

6.(1)(b) a letter authorizing the Minister to gain access to all information with respect to the product in the possession of Health Canada or of the government of any province or territory in Canada and authorizing the Minister to disclose any information with respect to the product in the possession of the Ministry to Health Canada or to the government of a province or territory in Canada;

Interpretation

As federal and provincial governments work to harmonize their drug review process, it is important that the Ministry to be able to communicate freely with other regulatory agencies. Manufacturers can satisfy this requirement by providing the Ministry permission, in writing, to access all product information filed with Health Canada and other regulatory agencies (i.e., provinces/territories). Letters should be:

- from the holder of the NOC; and
- dated and signed by a senior company official; and
- free of any restrictive clauses.

Points of Clarification

Only letters **free of any restrictions** will be accepted. The letter should authorize the Ministry to access any information pertaining to the drug product at any time. In the past, manufacturers included restrictions or limitations, such as notifying the manufacturer before obtaining information from Health Canada and or having a representative of the manufacturer present when the Ministry obtains information. A letter with any restrictions will not satisfy this requirement, and the submission will be deemed incomplete.

If a manufacturer is applying for the exemption under subsection 6.(3), the consent letter submitted under subsection 6.(1)(b) must be submitted by both the manufacturer making the submission, and the manufacturer of the original product. The Ministry requires this authorization to be able to access information on file at Health Canada, including the files of the original product.

When a third party is involved in filing a submission, a letter is required from all of the parties which may have information regarding the product on file with Health Canada – i.e., NOC holder, manufacturer, distributor, etc.

To assist manufacturers, the Ministry has developed a template letter, which is included on the next page; copies are also available in Part VI and on the Ministry's website. If manufacturers choose to use the template, they should ensure that it is printed on company letterhead, dated, and signed by an appropriate senior company official.

Template Letter of Consent
Allowing Communication with Health Canada, Provinces and Territories

[Manufacturer's letterhead]

[Date]

Director
Drug Programs Branch
Ministry of Health and Long-Term Care
3rd Floor, 5700 Yonge Street
Toronto, ON   M2M 4K5

Dear Director:

REFERENCE: *[Brand name/generic name, strength, and dosage form]*

This letter authorizes the Ontario Ministry of Health and Long-Term Care to gain access to all information with respect to the product in the possession of Health Canada or of the government of any province or territory in Canada. Furthermore, this letter authorizes the Minister to disclose any information with respect to the product in the possession of the Ministry to Health Canada or to the government of a province or territory in Canada.

[Signature]

[Name and Title of Senior Company Official]

6.(1)(c) documentation disclosing the product's master formulation;

Interpretation

If Health Canada has declared bioequivalence and the Canadian reference product on the NOC is identical to the Ministry's original product, this documentation is **not** required.

In all other cases, the Ministry will accept any of the following:

- completed Certified Product Information Document (CPID) that was approved by Health Canada; or
- master formulation (calculated per smallest unit).

Points of Clarification

If the manufacturer does not have a CPID approved by Health Canada, the Ministry will accept a copy of the originally approved master formulation for the drug product. The approved master formulation must contain the product name as described in the NOC, dated and signed by appropriate quality assurance persons. In cases where the product name described in the master formulation is different from the submitted product (e.g., different product name, different manufacturing source or manufacturer name, etc.), evidence is required to demonstrate the linkage between the product referred to in the master formulation and to the product submitted for listing.

For more information on the CPID, please refer to the **Drugs Directorate Policy: Guide on the Preparation of a Comprehensive Summary of Chemistry and Manufacturing Information and a Certified Product Information Document for New Drugs.**

Reference to another Ministry submission file is **not** acceptable.

In most cases, the information described above will be sufficient. However, if any questions arise during the screening/review process, the Ministry may ask manufacturers to submit more detailed information regarding the master formulation.

6.(1)(d) the proposed drug benefit price of the product;

Interpretation

The manufacturer should state clearly the proposed Drug Benefit Price (DBP) of each product for which they are seeking designation as interchangeable. The DBP should include, where applicable:

- price per smallest unit (e.g., tablet, capsule, gram or millilitre, etc); and

- price per smallest dispensable unit (e.g., kit, ampoule, prefilled syringe, vial combination package, etc.).

The DBP must comply with the pricing requirement outlined in subsection 7.(2) of Regulation 935 under the *Drug Interchangeability and Dispensing Fee Act*. For listing purposes, the DBP must be expressed to four decimal places ($0.0000). A submission with a price above the pricing requirement will be deemed incomplete. Refer to Section 7.(2) for more detail.

Points of Clarification

Where more than one DBP is proposed, then the lowest price will be used as the DBP, even if the higher price has met the pricing requirement.

When the manufacturer is seeking interchangeability for more than one package size (e.g., 10mL and 30mL vial), the submission should include the proposed DBP for each package size.

Please note that as of November 4, 1998, it is possible to consider a higher price for a drug product among other designated interchangeable products, if the submitted DBP exceeds the pricing requirement as outlined in subsection 7.(2) of Regulation 935 under the *Drug Interchangeability and Dispensing Fee Act*. That is, the submitted price is not less than or equal to 63% of the DBP for the original product currently listed in the Formulary/CDI.

If subsection 7.(2)2.i.B. or subsection 7.(2)2.ii.A. of the Regulation is to be applied to allow reference to a higher listed price either on or after March 31, 1994, please provide, in writing, the following information which was used to determine the submitted price:

- the name, strength and dosage form of the original product;

- the specific Formulary/CDI edition, and Supplement where applicable, and page number indicating when the original product was first listed;

- the specific listed price of the original product used in your calculation.

If the manufacturer is unable to provide the above information for a higher price, the calculated price will be as follows:

- For the first generic product in a category, the submitted DBP is less than or equal to 70 per cent (%) of the DBP for the original product as set out in the Formulary/CDI at the time the proposal is made to the Minister.

- For the second or subsequent generic product in a category, the submitted price is 63 per cent (%) of the DBP of the original product, as set out in the Formulary/CDI at the time the proposal is made to the Minister.

6.(1)(e) evidence that the manufacturer is able to supply the product at the proposed drug benefit price in a quantity sufficient to meet the anticipated demand for the product;

Interpretation

The manufacturer must be able to supply the drug product at the submitted price in a quantity sufficient to meet the anticipated demand. To satisfy this requirement, the manufacturer **must** submit a confirmation letter. The letter should:

- include confirmation of the ability to supply the product at the submitted price for distribution in a quantity sufficient to meet the anticipated demand; and

- be free of any conditions.

Points of Clarification

The Ministry does not allow conditional price increases.

To assist manufacturers, the Ministry has developed a template letter, which is included on the next page; copies are also available in Part VI and on the Ministry's website. If manufacturers choose to use the template, they should ensure that it is printed on company letterhead, dated, and signed by an appropriate senior company official.

Template Letter Confirming Ability to Supply Product at Proposed DBP

[Manufacturer's letterhead]

[date]

Director
Drug Programs Branch
Ministry of Health and Long-Term Care
3rd Floor, 5700 Yonge Street
Toronto, ON M2M 4K5

Dear Director:

REFERENCE: *[Brand name, generic name, strength, and dosage form]*

This letter is to confirm that *[name of manufacturer]* is currently able to supply the above drug product at the proposed Drug Benefit Price in a quantity sufficient to meet the anticipated demands for this product.

[Signature]

[Name and Title of Senior Company Official]

6.(1)(h) comparative bioavailability studies on humans, comparative clinical studies on humans, or both, or other in vivo studies that will show the interchangeability of the product with the original product;

Interpretation

This requirement **does not apply** to a drug product that has uncomplicated characteristics and is an oral dosage formulation used for systemic effects, or an oral modified release formulation, **if** that product has been designated as bioequivalent to the original product by Health Canada.

This requirement applies to all products that are **not declared bioequivalent** by Health Canada, and in all cases where the Canadian reference product differs from the Ministry's original product.

Manufacturers may satisfy this requirement by submitting the following:

- evidence of interchangeability (full reports of comparative bioavailability studies); and
- completed Bioequivalence Data Checklist; and
- completed Pharmacokinetic/Statistical Worksheet; and
- master formulation for the biolot.

This requirement also applies to **all Report C products**, regardless of whether the product has been declared bioequivalent to the original product by Health Canada.

Manufacturers may satisfy this requirement by submitting the following:

- evidence of interchangeability (full reports of comparative bioavailability studies); and
- completed Bioequivalence Data Checklist; and
- completed Pharmacokinetic/Statistical Worksheet.

Points of Clarification

Drug products that have uncomplicated characteristics and are oral dosage formulations used for systemic effects, or are oral modified release formulations, are described in the guidelines produced by Health Canada, **Conduct and Analysis of Bioavailability and Bioequivalence Studies - Part A: Oral Dosage Formulations used for Systemic Effects**

1992 and **Conduct and Analysis of Bioavailability and Bioequivalence Studies - Part B: Oral Modified Release Formulations**.

An "original product" is defined as the original source of a drug product in a particular strength and dosage form that is or was designated as a listed drug product under O. Reg. 201/96, or that was listed as a drug product under Regulation 868 of the Revised Regulations of Ontario, 1990 (General) or the Parcost C.D.I. prescribed under Ontario Regulation 839/84 as it read on the November 30, 1986.

Evidence of Interchangeability

Manufacturers can demonstrate bioequivalence with the original product by providing full reports of comparative bioavailability studies. **Raw data should not be submitted.** For more information on the conduct and analysis of bioavailability/bioequivalence studies, please consult the Drugs Directorate Guidelines, **Conduct and Analysis of Bioavailability and Bioequivalence Studies - Part A: Oral Dosage Formulations Used for Systemic Effects** and **Part B: Oral Modified Release Formulations.** The Ministry has harmonized its requirements for Guideline A and B drugs (i.e., those with uncomplicated characteristics and those with slow/extended drug release characteristics) with federal requirements.

With clinical studies, the Ministry requires the documentation outlined in regulation 12.(1)(h) of the *Ontario Drug Benefit Act*. See section 12.(1)(h) of the interpretive guidelines for details.

The submission must include the formulation of the multiple source products used in the studies.

Bioequivalence Data Checklist and Pharmacokinetic/Statistical Worksheet

The Bioequivalence Data Checklist and the Pharmacokinetic/Statistical Worksheet were developed based on the guidelines that DQTC reviewers use during their evaluation. They were designed to help manufacturers prepare submissions that are easy to review and ensure submissions proactively address the DQTC's usual questions.

For each question on the Bioequivalence Data Checklist, manufacturers should provide short answers below the question and direct reviewers to the supporting reference page(s). If a question on the Bioequivalence Data Checklist does not apply, please indicate not applicable (N/A) on the checklist and provide a rationale if necessary. A copy of the Bioequivalence Data Checklist and Pharmacokinetic/Statistical Worksheet are included at the end of this section; copies are also provided in Part VI and on the Ministry's website.

Bioequivalent, Identical Report C Drugs

When Health Canada has declared bioequivalence for a Report C drug, and the Canadian reference product is identical to the Ministry's original product, the Ministry will accept the following as evidence to support interchangeability:

- evidence of interchangeability (full reports of comparative bioavailability studies); and
- completed Bioequivalence Data Checklist; and
- completed Pharmacokinetic/Statistical Worksheet.

Although the Ministry will rely on the federal declaration of bioequivalence for the vast majority of products, full comparative bioavailability studies are required for Report C drugs (i.e., drugs that are toxic and/or possess complicated characteristics – pharmacokinetics/pharmacodynamics). When the Ministry receives a submission for a Report C drug, it will request from Health Canada a copy of the federal bioequivalence summary. No decision will be made until the Ministry reviews this summary, along with the submitted information.

Non-Bioequivalent and/or Non-Identical Drugs

When Health Canada has not declared bioequivalence or when the reference product is not identical to the Ministry's original product, the Ministry will accept the following as evidence to support interchangeability:

- evidence of interchangeability (full reports of comparative bioavailability studies); and
- completed Bioequivalence Data Checklist; and
- completed Pharmacokinetic/Statistical Worksheet; and
- master formulation for the biolot.

Solutions

If the manufacturer is seeking an interchangeability designation for a solution described under subsection 6.(5), subsections 6.(1)(h) and 6.(6) do not apply. The manufacturer must satisfy the requirements in subsections 6.(5) [physicochemical parameters for aqueous solutions] and 6.(1)(c) [master formulation]. For more information, please refer to subsections 6.(5) and 6.(1)(c) of these interpretive guidelines.

All Other Drug Products

For all other products that

- do not fall into the above categories, or
- do not have a declaration of bioequivalence, or
- have a declaration of bioequivalence with a reference product other than the Ministry's original product,

Manufacturers can demonstrate bioequivalence with the original product by providing full reports of comparative bioavailability studies.

If a comparative bioavailability study cannot be conducted (e.g., on drug products such as metered dose inhalers and ophthalmic suspensions), the Ministry may consider comparative pharmacodynamic/clinical studies of the product requested for listing and the original product, which compare efficacy and safety. In rare instances, a pharmacokinetic assessment in an appropriate animal study may provide evidence of interchangeability.

With pharmacodynamic and/or pharmacokinetic studies, the Ministry requires the following documentation:

(a) a detailed protocol, including a description of inclusion and exclusion criteria, subject numbers, demographics, and a discussion of the statistical analyses applied, including the statistical power of the study design; and

(b) evidence the protocol was approved for safety and ethics by a qualified, independent review committee; and

(c) all resulting data and appropriate analyses in a form suitable for scientific review.

Special Delivery Devices

If the manufacturer is seeking an interchangeability designation for a special delivery device, in-vitro testing is required to demonstrate comparable performance of special delivery devices used to deliver the therapeutic drug substance.

Manufacturers submitting **metered dose inhalers/nasal sprays** should provide comparative data for:

- description, colour, clarity and expiry; and
- pH, viscosity, surface tension, specific gravity, partition coefficient (where applicable); and
- particle size distribution; and
- consistent drug content per drop; and/or
- labelled potency claim per actuation; and

- spray pattern.

Manufacturers submitting **ophthalmic preparations or aqueous nasal sprays** should provide information demonstrating:

- comparative droplet size; and
- the delivery system disperses consistent and comparable amounts of drug per drop.

Please refer to subsection 6.(5) of these interpretive guidelines for more information relating to physicochemical parameters.

Further Points of Clarification

Original Product No Longer Listed

If a manufacturer is seeking interchangeability with an original product that was but is no longer listed, the cover letter accompanying the submission should clearly indicate the specific Formulary/CDI edition, supplement (where applicable), and page number indicating when the original product was listed.

Submitted vs. Bioequivalence Study Drug Product

In cases where the drug product used in the bioequivalence study is different from the submitted product (e.g., different product name, different manufacturing source or manufacturer name, etc.), evidence is required to demonstrate the linkage between the product used in the study and the product submitted for listing.

A letter confirming that the two formulations and manufacturing processes are identical, except for embossing and labelling, may be satisfactory. The letter should be dated and signed by a senior company official. Should questions arise, it may be necessary to provide further information including the master formulation and documentation regarding the manufacturing and quality control (e.g., production worksheets, Certificates of Analysis of active raw material/ finished products).

Submissions will be deemed incomplete and will remain as such until the Ministry has been satisfied that the linkage has been sufficiently established between the various products referred to in the submission.

Additional Strengths

When manufacturers submit several strengths of a specific dosage form concurrently or submit additional strengths of an already-listed drug product, they should refer to subsection 6.(4) to see if the exemption for additional strengths applies. If the exemption does not apply, manufacturers must submit separate comparative bioavailability or comparative clinical/pharmacodynamic studies for each strength of the drug product.

Where Health Canada has declared bioequivalence for one strength of a dosage form to the Ministry's original product, the Ministry will accept the declaration for all additional strengths. That is, the manufacturers will be exempt from providing comparative bioavailability studies for other strengths. The manufacturer should still provide the master formulation for all strengths as evidence of proportionality of the product composition.

If the formulations are not proportional, the comparative bioavailability studies for other strengths will be required.

Evaluation of Studies

In the case of pharmacodynamic studies, assessment is individualized and appropriate to the class of drugs under consideration. Manufacturers should ensure that pharmacodynamic studies are able, through both study design and sample size, to detect clinically important differences.

In the case of pharmacokinetic studies, the evaluation of interchangeability is generally based on three measures of bioavailability: AUC, Cmax, and Tmax.

Both the experimental and statistical evidence are evaluated by the DQTC. This examination may include the power of the study, the array of raw data, sample summary statistics and kinetic plots for individual subjects. Further analyses normally consist of statistical tests such as:

(a) t-test or ANOVA

(b) comparison of differences observed between means of the aforementioned measures (AUC, Cmax, and Tmax).

Notwithstanding the above, the Ministry may allow the acceptability criteria to be more or less stringent, depending on the clinical evidence.

Administrative details (refer to Part II of these guidelines for additional information):

- sturdy binders, not greater than three inches, should be used; and
- each binder should be clearly labelled; and
- a table of contents should be provided in each binder; and
- submissions should be paginated; and
- large, labelled tabs should be used.

BIOEQUIVALENCE DATA CHECKLIST

Product Name/Manufacturer: ______________________________

		Page Ref(s)
(a)	Executive summary of findings from the bioequivalence study (a short abstract giving the arguments for considering the products interchangeable), including a brief summary of the protocol, if available.	____________
(b)	Original study protocol.	____________
(c)	Date(s) and site of study.	____________
(d)	List of investigators and affiliations (CVs should be attached as appendix to study, as opposed to the main submission).	____________
(e)	List, with reasons, any protocol violations and/or missing values	____________
(f)	If requesting listing of more than one strength, indicate proportionality with tested strength; if not proportional, indicate if changes are significant, with supporting documentation.	____________
(g)	Description and method validation, including coefficient of variation, of the analytical method used in the bioavailability study.	____________
(h)	Pharmacodynamic data, if any, with appropriate statistical analysis and relationship to the pharmacokinetic data.	____________

Page Ref(s)

(i) Data on all subjects:

- age, sex and any other demographic information deemed relevant. ____________________
- AUCt, AUC's, Cmax, Tmax and any other pharmacokinetic parameters computed from potency corrected data for the drug products tested. ____________________
- time-concentration curve calculated with potency uncorrected data for each individual, for the drug products tested. ____________________
- adverse reactions, if any, tabulated by drug product. ____________________

(j) Data analysis:

- Means, standard deviations, coefficient of variations for each of the parameters, by drug product. ____________________
- Analysis of Variance used to derive the standard error in computing the confidence interval, including sources of variation for drug period, sequence and subjects within sequence. ____________________
- 90% confidence intervals on the appropriate scale for the ratios of the means for AUCt, AUC's, Cmax. ____________________
- A statement of conclusion and reasons for the conclusion. ____________________

(k) Other relevant data/information (please describe). ____________________

Note: The Ministry has harmonized its practices with the Therapeutic Product Programme (TPP) of Health Canada, and has the same statistical requirements for AUC and Cmax for drugs with uncomplicated characteristics. The following statistical requirements are used to assess the bioavailability studies for drugs with uncomplicated characteristics: confidence intervals for AUC at the 90% level, and comparison of mean Cmax values.

PHARMACOKINETIC/STATISTICAL WORK SHEET

Product Information	**Example**		
Name of drug product/metabolite	*MOH-Remarkable (MOH Inc)*		
Name of submitted product (Test)	*Remarkable (Brand Y Inc.)*	lot number:	expiry date:
Name of original product (Reference)	*Remarkable (Brand Y Inc.)*	lot number:	expiry date:
Strength/dosage form	*5mg USP Tablets*		

Reviewer:

AUC (0-T)	**Test Product** (Name/Strength/Dosage Form)	**Reference Product** (Name/Strength/Dosage Form)
Mean	*20.12*	*19.04*
Standard Deviation	*14.04*	*13.21*
Coefficient of Variation	*69.80*	*69.38*
Ratio of Means	*105 %*	
Mean of Ratios	*107 %*	
90% Confidence Interval (potency corrected)	*95 - 115 %*	

ANOVA (S/NS) Subject [*S*] Treatment [*N/S*] Sequence [*N/S*]

Distribution of individual ratios (# subjects test vs. ref.)	<0.7	0.7-0.8	0.8-0.9	0.9-1.1	1.1-1.2	1.2-1.3	>1.3
	2	*0*	*2*	*6*	*4*	*2*	*2*

AUC (0-∞)	**Test Product** (Name/Strength/Dosage Form)	**Reference Product** (Name/Strength/Dosage Form)
Mean	*21.54*	*20.39*
Standard Deviation	*14.24*	*13.37*
Coefficient of Variation	*66.11*	*65.57*
Ratio of Means	*105.0 %*	
Mean of Ratios	*107.0 %.*	
90% Confidence Interval (potency corrected)	*96.0 - 115.0 %*	

ANOVA (S/NS) Subject [*S*] Treatment [*N/S*] Sequence [*N/S*]

Distribution of individual ratios (# subjects test vs. ref.)	<0.7	0.7-0.8	0.8-0.9	0.9-1.1	1.1-1.2	1.2-1.3	>1.3
	2	*0*	*1*	*6*	*5*	*2*	*2*

Cmax	**Test Product** (Name/Strength/Dosage Form)	**Reference Product** (Name/Strength/Dosage Form)
Mean	*12.16*	*11.55*
Standard Deviation	*7.85*	*8.68*
Coefficient of Variation	*64.56*	*75.13*
Ratio of Means	*103.0 %*	
Mean of Ratios	*110.0 %*	
90% Confidence Interval (potency corrected)	*89.0 - 120.0 %*	

ANOVA (S/NS) Subject [*S*] Treatment [*N / S*] Sequence [*N / S*]

Distribution of individual ratios (# subjects test vs. ref.)	<0.7	0.7-0.8	0.8-0.9	0.9-1.1	1.1-1.2	1.2-1.3	>1.3
	3	*0*	*3*	*4*	*2*	*1*	*5*

Tmax	**Test Product** (Name/Strength/Dosage Form)	**Reference Product** (Name/Strength/Dosage Form)
Mean	*0.58*	*0.50*
Standard Deviation	*0.25*	*0.27*
Coefficient of Variation	*41.05*	*41.26*

6.(2) If Health Canada has not approved a product monograph for a drug product, the manufacturer of the product may, instead of submitting a copy of the product monograph as required under clause (1)(a), submit to the Minister the following information:

1. Pharmaceutical Information.
2. Information with respect to the product's clinical pharmacology.
3. Information as to the product's indications and clinical use.
4. A list of any contraindications, warnings or precautions in the use of the product and of possible adverse reactions to its use.
5. A list of symptoms of an overdose of the product and information as to the treatment of an overdose.
6. Information with respect to the dosage and administration of the product.
7. Information regarding the availability of dosage forms for each strength of the product marketed in Canada.

Interpretation

When a drug product was approved by Health Canada without an official product monograph (i.e., "old" drugs), the Ministry will accept the information generally included in the official product monograph in place of a product monograph. A manufacturer may submit a revised product monograph to satisfy this regulation.

Please refer to the **Drugs Directorate Guideline: Product Monograph** for more detail.

6.(3) Clauses (1)(c) and (h) do not apply to the manufacturer of a drug product if the dosage form, strength, formula and manufacturing process of the product and the testing standards for both the raw materials of the product and the finished product are identical to those of the product with which it seeks to be designated as interchangeable.

Interpretation

This regulation allows the manufacturer to submit a "pseudogeneric" drug product without the master formulation and comparative bioavailability data. **These drug products are made by the same manufacturer as a listed "original product".** This exemption applies only when the submitted drug product is **identical** to the "original product" with respect to physical and chemical properties, including:

- strength and dosage form;
- formulation including both active and inactive ingredients and their quantities;
- raw materials and finished product specifications.
- manufacturing processes;
- manufacturing site; and
- packaging format and size.

If a manufacturer can satisfy the conditions outlined above, it will be exempt from the 6.(1)(c) [master formulation] and 6.(1)(h) [comparative bioavailability/clinical studies]. Please note that the manufacturer must satisfy all the other applicable requirements under Section 6 of Regulation 935 under the *Drug Interchangeability and Dispensing Fee Act*.

Points of Clarification

"Original product" is defined as the original source of a drug product in a particular strength and dosage form that is or was designated as a listed drug product under O. Reg. 201/96 or that was listed as a drug product under Regulation 868 of the Revised Regulations of Ontario, 1990 (General) or the Parcost C.D.I. prescribed under Ontario Regulation 839/84 as it read on the November 30, 1986.

The NOC holder should submit a letter, dated and signed by a senior company official, to confirm that the product is identical in all chemistry and manufacturing aspects, except for embossing and labelling.

If a manufacturer is applying for this exemption, the consent letter submitted under subsection 6.(1)(b) should be from both the manufacturer filing the submission **and** the manufacturer of the "original product". The Ministry needs this to access all the information on file at Health Canada, including the files submitted for the "original product".

Note: The Ministry will not allow cross-referencing of its own submission files as retrieving archived files will delay the review process.

6.(4) A manufacturer may satisfy the condition set out in clause (1)(h) for a strength of a drug product by submitting the evidence referred to in clause (1)(h) for another strength of the same dosage form of the drug product if that information is sufficient for the purposes of evaluating the interchangeability of all the strengths of the dosage form of the product.

Interpretation

This exemption applies to the additional strengths, which are proportional to the strength submitted in the bioavailability studies.

Manufacturers who wish to use this exemption should provide:

- master formulations of all strengths, including the master formulation for the biolot; and
- evidence of bioequivalence (if formulations not proportional).

This exemption allows the comparative bioavailability/clinical data for one strength of a product to be considered to support other strengths of the same dosage form of the drug product. Manufacturers are required to provide the master formulations for all strengths. When a drug product does not qualify for this exemption, the manufacturer must submit separate comparative bioavailability/clinical studies for each strength of the drug product including the master formulation for all strengths.

Points of Clarification

The bioavailability/clinical study comparing the submitted multiple source products to the brand name product should be with the listed strength of the brand name product (i.e., the original product as defined by the regulations).

Evidence of proportionality in product composition or bioequivalence

If the other strengths have formulations that are **proportional** in product composition or have the same ingredients with only modest changes in the quantities of inactive ingredients as the strength(s) used in the comparative bioavailability/clinical data, a manufacturer may rely on the same comparative bioavailability/clinical data for the additional strengths of the drug product. The manufacturer should provide the master formulations for all the strengths as evidence of proportionality of the product composition.

If the additional strength of the product is **not proportional** in product composition, and major formulation differences exist between the strengths, the manufacturer should provide the following:

- master formulations for all strengths; and
- completed Bioequivalence Data Checklist; and
- completed Pharmacokinetic/Statistical Work Sheet; and
- evidence of bioequivalence; and
- master formulation for the biolot.

For more detail on the data required to demonstrate bioequivalence, please refer to the interpretation of subsection 6.(1)(h) of Regulation 935 under the *Drug Interchangeability and Dispensing Fee Act* in Part IIIB. The reference product used in the bioequivalence study must be the "original product". "Original product" is defined as the original source of a drug product in a particular strength and dosage form that is or was designated as a listed drug product under O. Reg. 201/96 or that was listed as a drug product under Regulation 868 of the Revised Regulations of Ontario, 1990 (General) or the Parcost C.D.I. prescribed under Ontario Regulation 839/84 as it read on the November 30, 1986.

Although the Ministry will consider the federal declaration of bioequivalence of a drug product, it will still require evidence of proportionality for additional strengths. That is, master formulations are required to determine the interchangeability of additional strength(s). Refer to 6(1)(c) for detailed information on the master formulation.

Where Health Canada has declared bioequivalence on the NOC for one strength of a dosage form to the Ministry's original product, the Ministry will accept the declaration for all additional strengths. That is, the exemption for a comparative bioavailability study will apply for all strengths. The manufacturer should still provide the master formulation for all strengths as evidence of proportionality of the product composition.

If the formulations are not proportional, the comparative bioavailability studies for other strengths will be required.

For more information on proportionality and bioequivalence, please refer to the **Drugs Directorate Policy: Bioequivalence of Proportional Formulations - Solid Oral Dosage Forms (January 19, 1996).**

Note: Manufacturers using this exemption to apply for additional strengths of an aqueous solution should address the comparative physicochemical data specified in subsection 6.(5) in their submissions. Please refer to subsection 6.(5) for more information.

6.(5) Clause (1)(h) does not apply with respect to a drug product that is pharmaceutically equivalent to the original product, demonstrates the same physicochemical properties of the original product, is the same dosage form, packaging format and volume as the original product and is one of the following:

1. A parenteral aqueous solution or a powder for reconstitution into an aqueous solution, that may be administered in an intravenous, intramuscular, subcutaneous or intrathecal fashion and that is in the same solvent and in the same concentration as the original product.
2. An oral solution, elixir, syrup or other similar solubilized form in the same concentration as the original product and which contains no ingredient that will affect the bioavailability of the active ingredient.
3. An ophthalmic, otic, nasal, rectal, vaginal or inhaled solution that is topical and aqueous.

Interpretation

For Guideline A, Guideline B and Report C drug products that are formulated as solutions (as noted above), manufacturers may be exempt from the requirements in subsection 6(1)(h) of Regulation 935 under the *Drug Interchangeability and Dispensing Fee Act*, as in-vitro studies may provide sufficient information to determine bioequivalence. Manufacturers should provide comparative physicochemical data to demonstrate the product's pharmaceutical equivalence with the original product. **This exemption does not apply for suspensions, emulsions, or oil-based injections or solutions.**

When this exemption applies, the manufacturer is required to submit:

6.(1)(a) evidence of Health Canada's approval:

- Notice of Compliance (NOC);and
- Drug Notification Form (DNF); and
- product monograph; and

6.(1)(b) consent letter; and

6.(1)(c) master formulation, and

6.(1)(d) proposed drug benefit price; and

6.(1)(e) letter confirming ability to supply; and

6.(5) comparative physicochemical parameters.

Comparative Physicochemical Parameters

Although the Ministry will consider the federal declaration of bioequivalence for a solution, it will still require the physicochemical data to evaluate interchangeability. **With this issue of the interpretive guidelines, the Ministry will allow the exemption for other oral solutions that are not aqueous solutions (i.e., alcohol-based solutions).**

In assessing the interchangeability designation of solutions, the DQTC has recommended manufacturers address the following test parameters:

- description (including colour, clarity, expiry date), and comparison with the reference product; and
- potency assay (drug concentration); and
- pH, viscosity, surface tension and specific gravity, and comparison with the reference product; and
- antimicrobial preservative assay and/or microbial challenge tests, as appropriate; and
- appropriate packaging; and
- partition coefficient or distribution constant of the drug, and comparison with the reference product if there are any excipients such as water soluble polymers, solvents or salts which may affect the bioavailability or therapeutic efficacy of the drug.

In addition to the above parameters, manufacturers should address other test parameters specific to the various dosage forms.

Drug Submission Screening Checklist for Aqueous Solutions

In light of the high rate of incomplete submissions, which are filed using exemption 6.(5), the Drug Submission Screening Checklist for Solutions found at the end of this section was developed to assist manufacturers; copies are also available in Part VI and on the Ministry's website. Where a specific test parameter is not assessed, manufacturers are advised to submit a rationale for the absence of the assessment. Submission for aqueous solutions will continue to be fully reviewed by the DQTC.

Interchangeability Testing Specifications

Testing should be from the **same** lot. Preferably, the tests should be conducted for a **current** lot of the drug product. The lot numbers and the expiry dates of the submitted and reference products must be provided. The test lot must be of the formulation marketed in Canada. Test results from a different lot may be accepted if the manufacturer provides evidence that the formulations are similar (i.e., the formulations of all lots should be submitted). The test documentation must include the information on the description of test, test specification and preferably method reference. The testing documentation should be dated and signed by a senior company official.

Test results from a lot up to one year post-expiry (as of the date of submission) may be accepted if the manufacturer provides evidence that the formulations are similar (i.e., the formulations of all lots should be submitted).

For solutions, the package size and package format must be identical and the container and closure should be similar in form and material to that of the listed original product. That is, a 1mL ampoule will not be considered for interchangeability designation with a 5 mL ampoule or 50mL vial of the original product.

The list of parameters, outlined under Comparative Physicochemical Parameters above and in the Drug Submission Screening Checklist for Solutions, is intended to help manufacturers provide sufficient data so that the Ministry can assess the submitted product on the basis of pharmaceutical equivalence. In the absence of published federal guidelines for the review of these products, DQTC will continue to fully review these products e.g. method of analysis. Although the list of parameters is intended to be comprehensive, during the course of the Ministry's/DQTC review, questions may arise and additional information may be requested. Manufacturers are encouraged to comply with these requests.

In submitting information on the test parameters, where summary tables of results are submitted, supporting documentation must be enclosed (i.e., certificates of analysis of submitted product or work sheets for the reference product). Manufacturers must provide information on all of the required parameters as specified under each type of solution. Where test results are not provided for a given parameter, the manufacturer must include a justification for the missing parameter, or the submission will be deemed incomplete.

DRUG SUBMISSION SCREENING CHECKLIST FOR AQUEOUS SOLUTIONS

Drug Product Information	Reference Product Information
Drug product:	**Reference product:**
Lot number:	**Lot number:**
Expiry date:	**Expiry date:**

Test Parameter	**Route of Administration**					
	Injectable	**Inhalation**	**Nasal**	**Ophthalmic**	**Oral ***	**Otic**
Description, colour, clarity, expiry	C	C	C	C	C	C
Drug Potency	NC	NC	NC	NC	NC	NC
Potency, preservative	NC	NC	NC	NC	NC	NC
Potency, salt, solvent	C	C	C	C	C	C
pH	C	C	C	C	C	C
Viscosity	C	C	C	C	C	C
Surface Tension	C	C	C	C	C	C
Specific Gravity	C	C	C	C	C	C
Antimicrobial Effectiveness Testing	NC	NC	NC	NC	NC	NC
Microbial Quality	n/a	n/a	NC	n/a	NC	NC
Partition Coefficient, where applicable	C	C	C	C	C	C
Sterility	NC	NC	C	NC	n/a	NC
Pyrogens, Endotoxin	NC	NC	n/a	n/a	n/a	n/a
Particulate Matter	NC	n/a	n/a	n/a	n/a	n/a
Foreign Matter	NC	NC	n/a	NC	n/a	NC
Fill Volume	NC	n/a	n/a	n/a	n/a	n/a
Uniformity of Mass	n/a	n/a	NC	n/a	NC	n/a
Osmolality, Osmolarity	C	C	C	C	n/a	C
Buffer Capacity	C	C	C	C	C	C
Droplet Size or Volume, Drug Content per Drop, Quantity per spray, as appropriate	n/a	C	C	C	n/a	C
Oral Drops Dose and Uniformity of Dose	n/a	n/a	n/a	n/a	C	n/a

C=comparative test; NC=non-comparative test; n/a=not applicable.

* orally administered solutions may be either aqueous or alcohol-based; all other solutions, regardless of the route of administration, must be aqueous.

6.(6)	Clause (1)(c) does not apply with respect to a product that has been designated as bioequivalent to the original product by Health Canada unless the product is described in subsection 6.(5).

Interpretation

When Health Canada has declared a drug product bioequivalent with the Ministry's original product, the manufacturer is required to submit:

6.(1)(a) evidence of Health Canada's approval:

- Notice of Compliance (NOC);and
- Drug Notification Form (DNF); and
- product monograph; and

6.(1)(b) consent letter; and

6.(1)(d) proposed drug benefit price; and

6.(1)(e) letter confirming ability to supply; and

6.(1)(h) evidence of interchangeability (only applicable to Report C drugs).

In an effort to harmonize its review efforts with Health Canada, the Ministry is accepting more fully the federal declaration of bioequivalence when making a designation of interchangeability. This will be possible where:

- bioequivalence is declared on the Notice of Compliance; and
- the Canadian reference product is identical to the Ministry's "original product".

When this exemption applies, the manufacturer may be exempt from providing:

6.(1)(c) master formulation; and

6.(1)(h) evidence of interchangeability for Guideline A and B drugs products as described in 6.(1)(h).

If the exemption does not apply, the manufacturer must satisfy all the requirements specified in Regulation 935, Section 6 under the *Drug Interchangeability and Dispensing Fee Act*.

If the product is described under subsection 6.(5), subsection 6.(6) does not apply. The manufacturer must comply with the requirement under subsection 6.(1) (c). To satisfy this requirement, the manufacturer may submit any of the following:

- the completed Certified Product Information Document (CPID) already prepared for and approved by Health Canada; or
- master formulation (calculated per smallest unit).

In the case where a manufacturer has a third party agreement as described in 6.(1), the master formulations are required for both of the submitted and the third party manufacturers.

Manufacturers seeking interchangeability of a solution described under subsection 6.(5) must provide comparative physicochemical testing in lieu of the evidence of bioequivalence. Please refer to subsection 6.(5) of the interpretive guidelines for more information on the physicochemical parameters.

Points of Clarification

"Original product" is defined as the original source of a drug product in a particular strength and dosage form that is or was designated as a listed drug product under O. Reg. 201/96 or that was listed as a drug product under Regulation 868 of the Revised Regulations of Ontario, 1990 (General) or the Parcost C.D.I. prescribed under Ontario Regulation 839/84 as it read on the November 30, 1986.

The Ministry will not allow cross-referencing to its own submission files as retrieving archived files will delay the review process.

6.(7) Clause (1)(h) does not apply with respect to a product that has been designated as bioequivalent to the original product by Health Canada if it is required to provide bioavailability studies to Health Canada under Part A or B of the guideline available from Health Canada and entitled "Conduct and Analysis of Bioavailability and Bioequivalence Studies".

Interpretation

This exemption applies to a drug product that has been designated as bioequivalent to the original product by Health Canada if that product has uncomplicated characteristics and is an oral dosage formulation used for systemic effects, or an oral modified release formulation. These are described in the guidelines produced by Health Canada, **Conduct and Analysis of Bioavailability and Bioequivalence Studies - Part A: Oral Dosage Formulations used for Systemic Effects 1992** or **Conduct and Analysis of Bioavailability and Bioequivalence Studies - Part B: Oral Modified Release Formulations**.

Points of Clarification

The Ministry intends to harmonize the provincial and federal review processes especially as they relate to the review of generic products. For generic products that have been declared as bioequivalent and have simple characteristics, that is Guideline A and Guideline B (commonly known as Report A and B) products, the Ministry will no longer require bioequivalence reports and these products will not be forwarded to DQTC for review. The Ministry will rely entirely on the federal declaration of bioequivalence for the purpose of determining the interchangeability of generic products with original products.

The Ministry will continue to require the bioavailability studies and review them for Report C products. Also, aqueous solutions will continue to be fully reviewed by the DQTC.

The manufacturer should clearly indicate in the submission cover letter the classification of the submitted drug product (i.e., Guideline A, B or Report C drug products).

7.(2) A strength and dosage form of a product shall not be designated as interchangeable with other products unless it meets the following conditions:

1. If the original product is a listed product and there are no other interchangeable products already designated, the drug benefit price of the product proposed to the Minister under clause 6.(1)(d) must be less than or equal to 70 per cent of the drug benefit price, as set out in Part III of the Formulary, of the product with which it would be interchangeable;

2. If the original product is a listed product and there are other interchangeable products already designated, the drug benefit price of the product proposed to the Minister under clause 6.(1)(d) must be,

    i. if the original product was listed as a listed drug product on or before March 31, 1994, less than or equal to the greater of the following amounts,

        A. 63 per cent of the drug benefit price of the original product, as set out in the Formulary at the time the proposal is made to the Minister under clause 6.(1)(d), or

        B. 63 per cent of the best available price of the original drug product, as set out in the Formulary on March 31, 1994, and if

    ii. if the original product was listed as a listed drug product after March 31, 1994, less than or equal to the greater of the following amounts:

        A. 63 per cent of the best available price or drug benefit price, as the case may be, of the original product, as set out in the Formulary at the time the original product was listed, or

        B. 63 per cent of the drug benefit price of the original product at the time the proposal is made to the Minister under clause 6.(1)(d),

    but in no event shall the drug benefit price of the proposed product be greater than the highest drug benefit price among the drug benefit prices set out in the Formulary for the products with which the proposed product would be interchangeable.

3. If the product is an original product that was but is no longer a listed drug product under Ontario Regulation 210/96 and if there are no other interchangeable products already designated, the drug benefit price of the product proposed to the Minister under clause 6.(1)(d) must be,

    i. less than or equal to 70 per cent of the drug benefit price of the original product that was set out in the Formulary immediately before its removal, or

    ii. if the original product was removed from the Formulary as a listed drug product before May 27, 1996, less that or equal to 70 per cent of the best available price that was set out in the Formulary immediately before the removal of the original product.

4. If the product is an original product that was but is no longer a listed drug product under Ontario Regulation 201/96 and if there are other interchangeable products already designated, the drug benefit price of the product proposed to the Minister under clause 6.(1)(d) must be,
   - i. less than or equal to 63 per cent of the drug benefit price of the original product that was set out in the Formulary immediately before its removal, or
   - ii. if the original product was removed from the Formulary as a listed drug product before May 27, 1996, less than or equal to 63 per cent of the best available price that was set out in the Formulary immediately before the removal of the original product.

Interpretation

For a drug product to be designated interchangeable, the proposed drug benefit price must comply with the pricing requirement described above. The regulation has been amended to allow for the pricing of multiple source products, which are being considered for interchangeability designation with original products that were once but are no longer listed. In these cases, the drug benefit price of the original product will be the price set out in the Formulary/CDI immediately prior to delisting.

For the first interchangeable product listing in a category

The submitted Drug Benefit Price (DBP) is less than or equal to 70 per cent (%) of the DBP for the original product as set out in the Formulary/CDI at the time the proposal is made to the Minister.

For the second or subsequent interchangeable listings in a category

The submitted price is 63 per cent (%) of the Dug Benefit Price of the original product, as set out in the Formulary/CDI at the time the proposal is made to the Minister.

If subsection 7.(2) 2.i.B. or subsection 7.(2)2.ii.A. is to be applied to allow reference to a higher listed price either on or after March 31, 1994, please provide, in writing, the following information which you used to determine your submitted price:

- the name, strength and dosage form of the original product; and
- the specific Formulary/CDI edition, and Supplement where applicable, and page number indicating when the original product was first listed; and
- the specific listed price of the original product used in your calculation.

8. The following conditions must be met in order for a drug product that has been designated as interchangeable to continue to be designated as interchangeable:

1. The manufacturer of the product shall give the Minister notice of changes to a product, including a formulation change, and of any change in the ownership of the manufacturer.
2. The product must be authorized for sale under the *Food and Drugs Act* (Canada).
3. The manufacturer of the product must continue to be able to supply the product at the drug benefit price in a quantity that is sufficient to meet the demand for the product.

Interpretation

To maintain a product listing, the manufacturer must comply with the conditions listed above.

Points of Clarification

Paragraph 1 of Section 8 ensures that the manufacturer notifies the Ministry of significant changes to drug products contained in the Formulary/CDI, and allows the Ministry to introduce changes, as appropriate, to the Formulary/CDI. The Ministry must be notified of changes to DIN, ownership of the manufacturer, significant changes to the product monograph, master formula where the changes are significant or affect the bioavailability of the drug product.

Manufacturers should clearly **indicate** which products are affected by the change. Manufacturers should not include those products that are currently not listed in the Formulary/CDI for notification of change. The Ministry will only acknowledge those products listed in the Formulary/CDI. The Ministry may return the list to manufacturers to identify the affected products before it proceeds in assessing the change.

Paragraph 2 of Section 8 ensures that for a drug to continue to be designated as a listed drug product, the manufacturer of the product must comply with Health Canada's requirements, including having a valid NOC and/or DIN and making the drug product in accordance with the regulations (e.g., the drug product is manufactured according to Good Manufacturing Practice standards).

Specific Applications of Paragraph 1 of Section 8

Notification of Change

The notification, dated and signed by the Chief Executive Officer or another senior company official, must be filed within 30 days after Health Canada has approved the change. The notification must include:

- identification of the change(s); and
- a brief explanation for the change(s); and
- confirmation that the bioavailability has not been affected; and
- evidence that Health Canada has approved the change (e.g., Notice of Compliance and/or Drug Notification Form and/or Letter of No Objection and/or Product Monograph, where applicable).

Change in DIN or Ownership

For a change in DIN or ownership, the notification should include:

- identification of the change(s); and
- a brief explanation for the change(s); and
- evidence that Health Canada has approved the change: (e.g., new NOC and/or Drug Notification Form and/or Letter of No Objection); and
- old and new DINs for the drug product, clearly identifying the strengths and dosage forms affected by the change.

Changes to the Product Monograph

Significant changes to the product monograph must be brought to the attention of the Ministry. Significant changes include any changes to indications, significant changes to contraindications, adverse effects and warning/precautions. For a change in product monograph or prescribing information, the notification should include:

- identification of the change(s); and
- a brief explanation for the change(s); and
- evidence that Health Canada has approved the change: (e.g., new NOC and/or Drug Notification Form or Letter of No Objection); and
- old and new DINs for the drug product, clearly identifying the strengths; and dosage forms affected by the change; and
- a copy of the new product monograph.

Changes in the Master Formulation

For major changes in the master formulation (changes which may affect the bioavailability of the product) the notification should include the old and new formulations and highlight the relevant differences:

- identification of the change(s); and
- a brief explanation for the change(s); and
- confirmation that the bioavailability has not been affected; and
- evidence that Health Canada has approved the change:
  (e.g., new NOC and/or Drug Notification Form or Letter of No Objection); and
- old and new DINs for the drug product, clearly identifying the strengths and dosage forms affected by the change (if applicable); and
- product monograph, if applicable.

Change Not Approved by Health Canada

If Health Canada has not approved the change (i.e.,"old" drugs), the manufacturer should submit documentation demonstrating that the bioavailability of the drug product was not affected. For a major change in the master formula, or for a major change in the finished product specifications for aqueous solutions, the Ministry will accept:

- identification of the change(s); and
- a brief explanation for the change(s); and
- old and new formulation with the differences highlighted; and
- justification why a bioavailability study is not required, or
- evidence of interchangeability of the old and new formulations.

Changes in Bioavailability

For changes in the bioavailability of a listed drug product, a new bioavailability study (or a justification for not providing a study) is required. Please refer to subsection 6.(1)(h) of Regulation 935 under the *Drug Interchangeability and Dispensing Fee Act* for more information on bioavailability evidence.

Note: The lists above identify information that should be sufficient in the majority of cases. Should questions arise, the Ministry may request the manufacturer to provide additional information as necessary. Manufacturers may also be required to confirm annually that all the information previously supplied about the drug listed in the Formulary/CDI is accurate and current. If issues or questions arise during the review process, the Ministry may request additional information.

PART IV

SUBMISSION GUIDELINES

FOR

DIABETIC TESTING AGENTS

Diabetic testing agents (i.e., blood glucose and urine ketone testing strips) are not considered drug products. Although a submission for a diabetic testing agent undergoes a similar review process as a drug product, the manufacturer must satisfy a different set of requirements to be considered for reimbursement according to the Maximum Allowable Reimbursement (MAR) mechanism and pricing schedule.

A Drug Quality and Therapeutics Committee (DQTC) consultant reviews the submission first. As with drug products, the DQTC as a whole is asked to make a final recommendation to the Ministry regarding the reimbursement of diabetic products. Please refer to the Formulary/CDI for more information on MAR and to Part II: Drug Submission Review Process for more detail on the review process.

The price per strip under the MAR mechanism in Part IX of the Formulary/Comparative Drug Index includes a mark up set by the Ministry. Please clearly indicate the following two prices: (1) the lowest price per unit sold to pharmacies and wholesalers (i.e., direct price without the mark up); and (2) the price including the wholesale mark up. The Ministry will add the mark up to the submitted unit if the testing strip is approved for the MAR schedule.

Submission Requirements

A manufacturer must include **two copies** of the administrative information and the following information when making a submission to the Ministry for a diabetic testing strips:
For a diabetic testing strip designed to measure glucose or ketones in the blood or urine to be considered for listing, the Ministry requires the following information:

- specifications for the finished product; and
- a sample of the label of the finished product as it is intended to be solid in Canada; and
- the lowest price per unit sold to pharmacies and wholesalers (with and without the mark-up); and
- a letter dated and signed by a senior company official confirming the ability to supply the product at the quoted price to meet the anticipated market demand; and
- ODB market share penetration or impact analysis on ODB expenditure, including the underlying assumptions for the calculation; and
- evidence of the product's precision, accuracy, variability and reliability over an appropriate range of values, and results from testing in patients (preferably in the elderly); and
- a copy of instructions (patient package insert, prescriber information/insert for the therapeutic use of the product).

PART V

SUBMISSION GUIDELINES FOR NUTRITION PRODUCTS

Nutrition products are not considered drug products. Although a submission for a nutrition product undergoes a similar review process as a drug product, the manufacturer must satisfy a different set of requirements to be considered for reimbursement according to the Maximum Allowable Reimbursement (MAR) mechanism and pricing schedule. In the case of nutrition products, a Drug Quality and Therapeutics Committee (DQTC) nutrition consultant first reviews the complete submission. As with drug products, the DQTC as a whole is asked to make a final recommendation to the Ministry regarding the reimbursement of nutrition products. Please refer to the Formulary/CDI for more information on MAR and to Part II: Drug Submission Review Process for more detail on the review process.

Please note that a nutrition product will not be reimbursed under the Ontario Drug Benefit program if:

- the product is advertised in Ontario to the public; or
- the distributor is not located in Canada and relies on a direct sales network; or
- the product is intended for the following uses:
- prescribed weight loss in the treatment of obesity
- food allergies
- body building
- meal replacement
- nutritional supplement
- convenience
- use as a replacement for breast feeding.

Submission Requirements

A manufacturer must include **two copies** of the administrative information and the following information when making a submission to the Ministry for a nutrition product:

- the completed Nutrition Product Work Sheet. A copy of this work sheet can be found at the back of this subsection; copies can also be found in Part VI: Template Letters, Checklists and Work Sheets, and on the Ministry's website.; and
- documentation with respect to complete ingredients, nutrient analysis of the product and the quantitative formula, including support for the classification of the nutrition product (e.g., polymeric, semi-elemental or elemental, or modular product); and
- daily volume to meet Recommended Nutrient Intake (RNI); and
- a sample of the label of the product as it is intended to be sold in Canada; and

- clearly indicate the following two prices: (1) the lowest price per unit sold to pharmacies and wholesalers (i.e., direct price without the mark up); and (2) the price including the wholesale mark up (and indicate percentage), for each package size of the product that is offered for sale, cost per 1000 kcal and cost per unit (mL or g); and

- documentation with respect to the indications of use; and

- **product specific** clinical studies and, if available, other clinical evidence of the product's therapeutic effectiveness or efficacy and of the product's safety, including any information that relates to adverse reactions. Comparative studies evaluating the product's therapeutic effectiveness or efficacy and the product's safety to that of other products or treatments is of particular interest.; and

- evidence demonstrating the benefit of the product in relation to the cost of the product and to any alternative products or treatments, if available.

A manufacturer must inform the Ministry of changes such as major formulation changes, changes in classification under the *Food and Drug Act*, changes in the ownership of the manufacturer, changes in product name, changes in advertising policy. For a major change in formulation, the manufacturer should submit:

- old and new quantitative formula and nutrient formulation with the differences highlighted; and

- evidence that changes are not significant enough to potentially alter clinical response or safety.

NUTRITION PRODUCT WORK SHEET

Product Information	
Product Name	
Name & Address of Manufacturer and/or Canadian distributor	

Please answer the following questions and complete the table below.

1. Is the product lactose-free?

2. Is the product advertised to the Ontario public now or will it be advertised to the Ontario public in the future?

3. How is the product classified for purposes of the regulations to the *Food and Drug Act* (e.g., formulated liquid diet)?

4. Under which Nutrition Product category in the Ontario Drug Benefit Formulary should the product be considered for listing?

Descriptive Item	Product Details	
Form *		
Package size *		
Kcal / g or mL		
Kcal / package		
g protein / g or mL		
g protein / package		

* Additional columns can be added if there are more than two forms (e.g., pudding, powder) or more than two package sizes of the product.

PART VI

TEMPLATE LETTERS, CHECKLISTS AND WORKSHEETS

This section contains the various template letters, checklists, and worksheets referred to throughout the submission guidelines.

The following templates are included in this section:

For submissions under DIDFA, Regulation 935, Section 6

All Submissions: DIDFA Submission Summary

6.(1)(b)	Consent Letter authorizing communication with Health Canada, Provinces, and Territories
6.(1)(e)	Letter confirming ability to supply
6.(1)(h)	Bioequivalence Data Checklist
6.(1)(h)	Pharmacokinetic/Statistical Work Sheet
6.(5)	Screening Checklist for Aqueous Solutions

For submissions under ODBA, O.Reg. 201/96, Section 12

All Submissions: ODBA Submission Summary

12.(1)(b)	Consent Letter authorizing communication with Health Canada, Provinces, and Territories
12.(1)(e)	Letter confirming ability to supply
12.(1)(h)	Clinical Data Checklist
12.(1)(i)	Pharmacoeconomic Analysis Summary Pharmacoeconomic Analysis Work Sheet ODB Financial Impact Analysis Summary
12.0.1(1)	Written Agreement Template

SUBMISSION SUMMARY
For Submissions under DIDFA, Regulation 935, Section 6

Drug Products (Brand name/generic name/strengths):

Original Drug Product (to which interchangeability designation is sought)

Submitting Manufacturer:

Please complete all items

Submission Type

1. Submission Type (select one): **First Review** ☐
   - Second Review ☐ Master File #: M
   - Reconsideration ☐ Master File #: M
   - Meeting Request ☐ Master File #: M

2. Category/Designation
   - a) Submission category (select one)
     - New Product ☐
     - New Strength ☐
     - New Indication ☐
     - New Dosage ☐
     - New Format ☐
     - Notice of Change ☐
   - b) If applicable, list Formulary designation sought:
     - Interchangeable ☐
     - Facilitated Access ☐
     - Section 8 ☐

Fast Track Request

Page Ref.

		No	Yes
3. a) Request for a "fast track" review for this submission:	☐	☐	( )
b) Justification provided for "fast track" request:	☐	☐	( )

Source and Authorization for Submission

4. a) Submitting manufacturer of the submission indicated:			( )
b) Is the submitting manufacturer the holder of the NOC? *If not, provide information for 4. (c) and (d)*	☐	☐	( )
c) Letter from NOC holder authorizing submitting manufacturer to submit on NOC holder's behalf:	☐	☐	( )
d) Relationship between each party detailed:	☐	☐	( )

SUBMISSION SUMMARY – PAGE 2

Administrative Issues

	No	Yes	Page Ref.
5. a) **Two** complete sets of the submission provided:	☐	☐	
b)Number of binders that make up each set of a submission:			( )
c) Submission is well organized, tabbed and indexed according to the relevant section of the requirements:	☐	☐	
d) A table of contents is included in the submission:	☐	☐	

Submission Data

6. a) Schedule of drug classification:

Guideline A ☐
Guideline B ☐
Report C ☐

b) Drug status: New Drug ☐
Old Drug ☐

7. If applicable, specify which exemptive regulations were applied for:

6.(2) ☐ **6.(5)** ☐
6.(3) ☐ **6.(6)** ☐
6.(4) ☐ **6.(7)** ☐

Interchangeability Information

	No	Yes	Page Ref.
8. a) Bioequivalence declared to the Canadian Reference Product on the NOC:	☐	☐	( )
b) Reference product is the same as the Ministry's original product	☐	☐	( )
c) Reference product is currently listed in the Formulary/CDI:	☐	☐	

d) If reference product is not currently listed in the Formulary/CDI, specify the edition, supplement, and page number indicating when the original product was first listed.

Edition: ( )
Supplement: ( )
Page: ( )

Bioavailability Data

	No	Yes	Page Ref.
9. a) Bioavailability study report provided:	☐	☐	( )
If not, please provide justification/exemption:			( )
b) Bioavailability test lots have the same formulation as the submitted lot:	☐	☐	( )
c) Clarification/evidence provided of linkage if product names different in (b)	☐	☐	( )

Template Letter of Consent
Allowing Communication with Health Canada, Provinces and Territories

[Manufacturer's letterhead]

[Date]

Director
Drug Programs Branch
Ministry of Health and Long-Term Care
3rd Floor, 5700 Yonge Street
Toronto, ON   M2M 4K5

Dear Director:

REFERENCE: *[Brand name/generic name, strength, and dosage form]*

This letter authorizes the Ontario Ministry of Health and Long-Term Care to gain access to all information with respect to the product in the possession of Health Canada or of the government of any province or territory in Canada. Furthermore, this letter authorizes the Minister to disclose any information with respect to the product in the possession of the Ministry to Health Canada or to the government of a province or territory in Canada.

[Signature]

[Name and Title of Senior Company Official]

Template Letter Confirming Ability to Supply Product at Proposed DBP

[Manufacturer's letterhead]

[date]

Director
Drug Programs Branch
Ministry of Health and Long-Term Care
3rd Floor, 5700 Yonge Street
Toronto, ON   M2M 4K5

Dear Director:

REFERENCE: *[Brand name, generic name, strength, and dosage form]*

This letter is to confirm that *[name of manufacturer]* is currently able to supply the above drug product at the proposed Drug Benefit Price in a quantity sufficient to meet the anticipated demands for this product.

[Signature]

[Name and Title of Senior Company Official]

BIOEQUIVALENCE DATA CHECKLIST

Product Name/Manufacturer: ____________________

Page Ref(s)

(d) Executive summary of findings from the bioequivalence study (a short abstract giving the arguments for considering the products interchangeable), including a brief summary of the protocol, if available. ____________

(e) Original study protocol. ____________

(f) Date(s) and site of study. ____________

(d) List of investigators and affiliations (CVs should be attached as appendix to study, as opposed to the main submission). ____________

(e) List, with reasons, any protocol violations and/or missing values ____________

(f) If requesting listing of more than one strength, indicate proportionality with tested strength; if not proportional, indicate if changes are significant, with supporting documentation. ____________

(g) Description and method validation, including coefficient of variation, of the analytical method used in the bioavailability study. ____________

(h) Pharmacodynamic data, if any, with appropriate statistical analysis and relationship to the pharmacokinetic data. ____________

Page Ref(s)

(i) Data on all subjects:

- age, sex and any other demographic information deemed relevant. ______________
- AUCt, AUC's, Cmax, Tmax and any other pharmacokinetic parameters computed from potency corrected data for the drug products tested. ______________
- time-concentration curve calculated with potency uncorrected data for each individual, for the drug products tested. ______________
- adverse reactions, if any, tabulated by drug product. ______________

(j) Data analysis:

- Means, standard deviations, coefficient of variations for each of the parameters, by drug product. ______________
- Analysis of Variance used to derive the standard error in computing the confidence interval, including sources of variation for drug period, sequence and subjects within sequence. ______________
- 90% confidence intervals on the appropriate scale for the ratios of the means for AUCt, AUC's, Cmax. ______________
- A statement of conclusion and reasons for the conclusion. ______________

(k) Other relevant data/information (please describe). ______________

Note: The Ministry has harmonized its practices with the Therapeutic Product Programme (TPP) of Health Canada, and has the same statistical requirements for AUC and Cmax for drugs with uncomplicated characteristics. The following statistical requirements are used to assess the bioavailability studies for drugs with uncomplicated characteristics: confidence intervals for AUC at the 90% level, and comparison of mean Cmax values.

PHARMACOKINETIC/STATISTICAL WORK SHEET

Product Information	**Example**
Name of drug product/metabolite	*MOH-Remarkable (MOH Inc)*
Name of submitted product (Test)	*Remarkable (Brand Y Inc.)* lot number: expiry date:
Name of original product (Reference)	*Remarkable (Brand Y Inc.)* lot number: expiry date:
Strength/dosage form	*5mg USP Tablets*

Reviewer:

AUC (0-T)	**Test Product** (Name/Strength/Dosage Form)	**Reference Product** (Name/Strength/Dosage Form)
Mean	*20.12*	*19.04*
Standard Deviation	*14.04*	*13.21*
Coefficient of Variation	*69.80*	*69.38*
Ratio of Means	*105 %*	
Mean of Ratios	*107 %*	
90% Confidence Interval (potency corrected)	*95 - 115 %*	

ANOVA (S/NS) Subject [*S*] Treatment [*N / S*] Sequence [*N / S*]

Distribution of individual ratios (# subjects test vs. ref.)	<0.7	0.7-0.8	0.8-0.9	0.9-1.1	1.1-1.2	1.2-1.3	>1.3
	2	*0*	*2*	*6*	*4*	*2*	*2*

AUC (O-∞)	**Test Product** (Name/Strength/Dosage Form)	**Reference Product** (Name/Strength/Dosage Form)
Mean	*21.54*	*20.39*
Standard Deviation	*14.24*	*13.37*
Coefficient of Variation	*66.11*	*65.57*
Ratio of Means	*105.0 %*	
Mean of Ratios	*107.0 %.*	
90% Confidence Interval (potency corrected)	*96.0 - 115.0 %*	

ANOVA (S/NS) Subject [*S*] Treatment [*N / S*] Sequence [*N / S*]

Distribution of individual ratios (# subjects test vs. ref.)	<0.7	0.7-0.8	0.8-0.9	0.9-1.1	1.1-1.2	1.2-1.3	>1.3
	2	*0*	*1*	*6*	*5*	*2*	*2*

Cmax	**Test Product** (Name/Strength/Dosage Form)	**Reference Product** (Name/Strength/Dosage Form)
Mean Standard Deviation Coefficient of Variation	*12.16* *7.85* *64.56*	*11.55* *8.68* *75.13*
Ratio of Means Mean of Ratios	*103.0 %* *110.0 %*	
90% Confidence Interval (potency corrected)	*89.0 - 120.0 %*	

ANOVA (S/NS) Subject [*S*] Treatment [*N / S*] Sequence [*N / S*]

Distribution of individual ratios (# subjects test vs. ref.)	<0.7	0.7-0.8	0.8-0.9	0.9-1.1	1.1-1.2	1.2-1.3	>1.3
	3	*0*	*3*	*4*	*2*	*1*	*5*

Tmax	**Test Product** (Name/Strength/Dosage Form)	**Reference Product** (Name/Strength/Dosage Form)
Mean Standard Deviation Coefficient of Variation	*0.58* *0.25* *41.05*	*0.50* *0.27* *41.26*

DRUG SUBMISSION SCREENING CHECKLIST FOR AQUEOUS SOLUTIONS

Drug Product Information	Reference Product Information
Drug product:	**Reference product:**
Lot number:	**Lot number:**
Expiry date:	**Expiry date:**

Test Parameter	**Route of Administration**					
	Injectable	**Inhalation**	**Nasal**	**Ophthalmic**	**Oral ***	**Otic**
Description, colour, clarity, expiry	C	C	C	C	C	C
Drug Potency	NC	NC	NC	NC	NC	NC
Potency, preservative	NC	NC	NC	NC	NC	NC
Potency, salt, solvent	C	C	C	C	C	C
pH	C	C	C	C	C	C
Viscosity	C	C	C	C	C	C
Surface Tension	C	C	C	C	C	C
Specific Gravity	C	C	C	C	C	C
Antimicrobial Effectiveness Testing	NC	NC	NC	NC	NC	NC
Microbial Quality	n/a	n/a	NC	n/a	NC	NC
Partition Coefficient, where applicable	C	C	C	C	C	C
Sterility	NC	NC	C	NC	n/a	NC
Pyrogens, Endotoxin	NC	NC	n/a	n/a	n/a	n/a
Particulate Matter	NC	n/a	n/a	n/a	n/a	n/a
Foreign Matter	NC	NC	n/a	NC	n/a	NC
Fill Volume	NC	n/a	n/a	n/a	n/a	n/a
Uniformity of Mass	n/a	n/a	NC	n/a	NC	n/a
Osmolality, Osmolarity	C	C	C	C	n/a	C
Buffer Capacity	C	C	C	C	C	C
Droplet Size or Volume, Drug Content per Drop, Quantity per spray, as appropriate	n/a	C	C	C	n/a	C
Oral Drops Dose and Uniformity of Dose	n/a	n/a	n/a	n/a	C	n/a

C=comparative test; NC=non-comparative test; n/a=not applicable.

* orally administered solutions may be either aqueous or alcohol-based; all other solutions, regardless of the route of administration, must be aqueous.

SUBMISSION SUMMARY
For Submissions under ODBA, O. Reg. 201/96, Section 12

Drug Products (Brand name/generic name/strengths):

Submitting Manufacturer:

Submission Type

1. **Submission Type (select one)**

First Review ☐
Second Review ☐ Master File #: M
Reconsideration ☐ Master File #: M
Meeting Request ☐ Master File #: M

2. **Category/Designation**

a) Submission category (select one)

New Product ☐
New Strength ☐
New Indication ☐
New Dosage ☐
New Format ☐
Notice of Change ☐

b) If applicable, list Formulary designation sought:

General Benefit ☐
Limited Use ☐
Section 8 ☐

Fast Track Request

	No	Yes	Page Ref.
3. a) Request for a "fast track" review for this submission:	☐	☐	( )
b) Justification provided for "fast track" request:	☐	☐	( )

Source and Authorization for Submission

4. a) Submitting manufacturer of the submission indicated:			( )
b) Is the submitting manufacturer the holder of the Notice of Compliance? *If not, provide information for 4. (c) and (d)*	☐	☐	( )
c) Letter from NOC holder authorizing submitting manufacturer to submit on NOC holder's behalf:	☐	☐	( )
d) Relationship between each party detailed:	☐	☐	( )

Administrative Issues

5. a) **Three** complete sets of the submission provided:	☐	☐	
b) Number of binders that make up each set of a submission:			( )

SUBMISSION SUMMARY – PAGE 2

	No	Yes	Page Ref.
c) Submission is well organized, tabbed and indexed according to the relevant section of the requirements:	☐	☐	
d) A table of contents is included in the submission:	☐	☐	

Submission Data

6. a) Schedule of drug classification:

Guideline A ☐
Guideline B ☐
Report C ☐

b) Drug status: New Drug ☐
Old Drug ☐

7. If applicable, specify which exemptive regulations were applied for:

12.(2) ☐
12.(3) ☐
12.(3.1) ☐
12.(4) ☐

		No	Yes	Page Ref.
8.	a) Clinical trials were conducted on the *submitted* product:	☐	☐	( )
	If not, please specify and provide justification:			( )
	b) Where the name(s) of products evaluated in clinical trials differs from that of the submitted product, clarification/evidence linking the data to the submission is provided:	☐	☐	( )
9.	a) Pharmacoeconomic analysis provided:	☐	☐	( )
	If no, please provide justification:			( )
	b) Three year budget impact analysis provided:	☐	☐	( )
	c) Pharmacoeconomic analysis summary provided:	☐	☐	( )

Template Letter of Consent
Allowing Communication with Health Canada, Provinces and Territories, and PMPRB

[Manufacturer's letterhead]

[Date]

Director
Drug Programs Branch
Ministry of Health and Long-Term Care
3rd Floor, 5700 Yonge Street
Toronto, ON M2M 4K5

Dear Director:

REFERENCE: *[Product name/generic name, strength, and dosage form]*

This letter authorizes the Ontario Ministry of Health and Long-Term Care to gain access to all information with respect to the product in the possession of Health Canada or of the government of any province or territory in Canada or the Patented Medicine Prices Review Board (PMPRB). Furthermore, this letter authorizes the Minister to disclose any information with respect to the product in the possession of the Ministry to Health Canada or to the government of a province or territory in Canada or the PMPRB.

[Signature]

[Name and Title of Senior Company Official]

Template Letter Confirming Ability to Supply Product at Proposed DBP

[Manufacturer's letterhead]

[Date]

Director
Drug Programs Branch
Ministry of Health and Long-Term Care
3rd Floor, 5700 Yonge Street
Toronto, ON M2M 4K5

Dear Director:

REFERENCE: *[Product name, generic name, strength and dosage form]*

This letter is to confirm that *[name of manufacturer]* is currently able to supply the above drug product at the proposed Drug Benefit Price in a quantity sufficient to meet the anticipated demands for this product.

[Signature]

[Name and Title of Senior Company Official]

CLINICAL DATA CHECKLIST

Product Name/Manufacturer: ____________________________________

Page Ref(s)

Drug Product

1. What is the pharmacological mechanism of the drug? ____________

2. What are the drug's Health Canada approved indications? ____________

3. What is the recommended dose range and duration of therapy? (Please include relevant patient populations - e.g., the elderly) ____________

5. What Formulary/CDI listing status is proposed by the manufacturer? ____________

Clinical Evidence

1. What are the conclusions of randomized controlled trials supporting the efficacy (i.e. when used under optimal circumstances) of the product? Are trials published in peer-reviewed journals? ____________

2. What are the key comparators for this drug product? Which ones are listed in the Formulary/CDI? ____________

3. What are the results of randomized trials comparing the product to listed alternatives on the Formulary/CDI? Are there randomized trials comparing the product to the least costly and most widely used alternative products listed in the Formulary/CDI? ____________

4. What are the conclusions of randomized controlled trials supporting the effectiveness (i.e., when used under usual, real world circumstances) of the product? Are trials published in peer-reviewed journals? ____________

5. Do the randomized trials use the most clinically relevant outcome measures, or do they use the surrogate outcomes requiring extrapolation to the relevant outcome? Are the end-point(s) sufficiently justified? ____________

6. Were any clinical studies conducted in the elderly, women and children? If not, why not? ____________

7. Were any of the clinical trials conducted in Canada? ____________

Page Ref(s)

8. Are there ongoing trials that would provide additional information on the product? __________

9. What are the contraindications for the product? __________

10. What are the side effects of the drug product? __________

11. Are there particular safety issues of concern to recipients of the ODB program (e.g., safety in the elderly, women and children)? __________

12. If the product contains a combination of drugs, is there a pharmacologic and pharmacokinetic rationale for the combination? Specifically, does each component of the combination make a contribution to the claimed effect(s)? Is the dose of each component appropriate for the elderly and/or children? Is the effect of either component modified (synergistically or antagonistically) by the addition of the other component? __________

Drug Utilization

1. What are the Health Canada approved patient population group(s) for the drug? __________

2. Will clinicians be able to easily and precisely determine which patients should be treated with this drug? Please explain. __________

3. Are there other clinical uses or trials for non-approved Health Canada indications? __________

4. Is it likely that clinicians will expand the use of the product for conditions not approved by Health Canada? If not, what is the evidence to support this position? __________

5. What is the projected number of patients in Ontario covered by ODB who will use the product in a year? __________

6. Are there utilization data for the drug product in other jurisdictions? If so, please discuss the possible utilization impact for ODB. __________

PHARMACOECONOMIC ANALYSIS SUMMARY

SECTION I. DRUG PRODUCT

Product Information	
Brand Name / Manufacturer	*Drug X Tablet USP (ACME Ltd.)*
Generic Name / Strength / Dosage Form	*Generic C 5 mg Tablet*
DIN	*01234567*
Usual Dose Regimen/Duration	*5 mg bid x 10 days*
Submitted Price Per Unit	*$2.00 per tab*
Daily Cost *	*$ 4.00 per day*

* based on usual dosing regimen and submitted price, as stated above

Available Package Size (A)	Price (B)	Calculated Price/Unit (C = B/A)	Cost of Usual Dosing Regimen
50	*$ 100.00*	*$ 2.00 per tablet*	*$ 40.00*
100	*$200.00*	*$ 2.00 per tablet*	*$ 40.00*
500	*$ 1000.00*	*$ 2.00 per tablet*	*$ 40.00*

SECTION II. COMPARATOR DRUG PRODUCT / TREATMENT

Please indicate all appropriate drug comparators (including strength and dosage form) and/or treatment comparators for this product.

Generic Name (Mfr) / Strength / Dosage Form	Price *	Equivalent Dosing Regimen for Comparator	Daily Cost	Cost of Usual Dosing Regimen
Generic A (Brand Y Inc) 5 mg USP tab	*$1.00*	*5 mg bid x 10 days*	*$2.00*	*$20.00*
Generic B (Brand Z Inc) 5 mg BP cap	*$1.50*	*5 mg tid x 7 days*	*$4.50*	*$31.50*

* indicate source if other than the price in the Formulary/CDI.

SECTION III. COMPARATIVE OUTCOMES

Drug	Outcome 1 (e.g. successes)	Outcome 2 (e.g. adverse events)	Outcome 3 (e.g. deaths)	Outcome 4 (e.g. projected survival)
Drug X	***$ 70%***	***5%***	***1%***	***20 years***
Generic A	*$ 80%*	*10%*	*2%*	*18 years*
Generic B	*$ 70%*	*10%*	*3%*	*16 years*

References:

Note:

- Appropriate comparators should be listed for each strength and dosage form.
- The manufacturer should indicate comparable dosing regimens, including the duration of therapy.
- Where there are multiple source alternatives for the products, the lowest cost interchangeable alternatives should be listed first.
- Where there are listed single source alternatives for the product, these may also be listed.
- Where there are no appropriate listed single or multiple source alternatives, other marketed drug products may be listed.
- Where the appropriate comparison is not a drug but another treatment, please attach a separate sheet outlining the treatment and indicating why it is the appropriate comparator.

SECTION IV. PHARMACOECONOMIC ANALYSIS

Pharmacoeconomic Analysis included? [X] Yes [ ] No

Pharmacoeconomic Worksheet included? [X] Yes [ ] No

If yes, please indicate type of analysis:
[ ] Cost-Minimization
[ ] Cost-Consequence
[X] Cost-Effectiveness
[ ] Cost-Utility
[ ] Cost-Benefit

If a detailed economic analysis is **not** included, please outline the reasons below:

PHARMACOECONOMIC ANALYSIS WORK SHEET

Product Information	
Drug Product (generic name/strength/dosage form)	*Drug X Tablet USP* *Generic C 5 mg Tablet*
Name of Manufacturer	*ACME Ltd.*

Please complete each of the following questions:

1. (a) What is the question being asked in the analysis?

   (b) What type of economic analysis was performed to answer the question?

   i Cost comparison
   ii. Cost-consequence analysis
   iii. Cost-effectiveness analysis
   iv. Cost-utility analysis
   v. Cost-benefit analysis

   (c) What is the justification for the approach taken?

2. (a) Did the study involve a comparison of alternative treatments for patients with the same clinical condition?

   (b) Are those alternatives explicitly stated?

   (c) Is the analysis therefore an incremental analysis?

3. (a) Is the viewpoint or perspective for the analysis stated clearly?

   (b) Is it a societal perspective, third-party payer perspective, patient perspective?

   (c) Is the analysis presented in a disaggregated fashion showing these perspectives separately?

4. (a) Was the evidence of the product's efficacy established through randomized trials?

   (b) Was this evidence of efficacy supplemented by evidence of effectiveness applicable to the patients covered by the Ontario Drug Benefit program?

   (c) Was the latter evidence derived from studies documenting routine use in clinical practice?

5. (a) Are the methods and analysis displayed in a clear and transparent manner?

   (b) Are the components of the numerator (cost of each alternative) and denominator (clinical outcomes of each alternative) displayed?

   (c) Are clinical outcomes expressed first in natural units and then translated into alternative units such as benefits or utility? (See Section 3.4.d. of the *Ontario Guidelines for Economic Analysis of Pharmaceutical Products* for suggested format).

6. Are all important and relevant costs and consequences (outcomes), including adverse effects, for each alternative identified?

7. (a) Are costs and consequences modelled as in a decision tree with information derived from a variety of sources; OR
   (b) estimated directly from a variety of sources; OR
   (c) estimated directly from a specific patient population?

8. (a) Are capital costs and overhead costs included as well as operating costs?
   (b) How were they measured?

9. How were indirect costs identified and estimated?

10. How was quality of life measured?

11. (a) What equity assumptions were made in the analysis?
   (b) For example, are QALYs gained by any individual considered equal?

12. (a) If some variables were difficult to measure, how did the authors handle this difficulty?
   (b) Did they slant the analysis all in favour of one intervention in order to bias the analysis against the desired result?

13. (a) Were extensive sensitivity analyses performed?
   (b) What were the ranges of values for variables in the sensitivity analyses?

14. (a) Is quality of life an important component of an economic analysis of this question?
   (b) How sensitive is the estimate of cost utility to variations in quality of life?

15. (a) Is there an estimate of the aggregate incremental expenditure required for the province to provide this product to patients covered by its programs?
   (b) What is the estimate of aggregate incremental costs?
   (c) Does this estimate cover all of the major indications for use of the product?

16. (a) Has the incremental cost-effectiveness ratio been estimated for a special clinical indication that represents the majority or all of its expected use by those covered under the Ontario Drug Benefit program?
   (b) Do these other indications involve a large amount of utilization for which the ratio may be very different?

17. (a) Who performed the analysis?

    (b) Did the authors of the report sign a letter indicating their agreement with the entire document presented?

    (c) Does the report indicate that the authors had independent control over the methods and right to publish the analysis regardless of its results?

18. What is the "bottom line" result of the analysis in quantitative terms? The answer to this question will be statements like the following:

    - The cost per QALYs gained for using this product compared to the alternative is $X, or ranges from $Y to $Z.
    - The use of this product compared to the stated alternative will result in an expected incremental expenditure of $X per patient treated with a net reduction of Y major adverse clinical events (e.g., cardiac deaths) and Z minor clinical events (e.g., side effects).

ODB FINANCIAL IMPACT ANALYSIS SUMMARY

SECTION I. DRUG PRODUCT

Product Information	
Drug Name / Manufacturer	
Generic Name / Strength / Dosage Form	
Proposed reimbursement status	
DIN	
Submitted Price Per Unit	
Daily Cost *	
Usual Dosing Regimen/Duration	
Maximum Dosing Regimen/Duration	

* based on usual dosing regimen and submitted price, as stated above.

SECTION II. SUMMARY OF ODB FINANCIAL IMPACT

Summary Item	Manufacturer's Submitted Estimates		
	Year 1	Year 2	Year 3
Drug Cost* ($)			
Claims			
Net Expenditure/(Savings)			

* Drug Cost should exclude up-charge and professional fee.

SECTION III: UNDERLYING ASSUMPTIONS FOR KEY FACTORS IN FORECAST – MOST LIKELY SCENARIO

For each parameter, it would be helpful to organize the data according to Baseline (where applicable), Year 1, Year 2, and Year 3 with the confidence level (high, medium or low) and the evidence/data sources.

Parameter	Baseline	Year 1	Year 2	Year 3	Confidence Level (high/med/low)	Evidence used to support assumptions
1. Disease Demographics						
(e.g. number of patients with the disease, number of patients consulting physicians, number of patients diagnosed, number of patients treated, number of ODB recipients)						
2. Market Share For (1) submitted product; (2) comparators within therapeutic class; (3) other relevant comparators for therapeutic indication.						
a) Patients (e.g. new patients, patients switching from competitor products)						
b) Claims (e.g. claims/ patient, claims/year)						
3. Growth Rate (e.g., compliance rate, withdrawal rate, potential impact of future listings such as new generic products)						
4. ODB Expenditures For (1) submitted product; (2) comparators within therapeutic class; (3) other relevant comparators for therapeutic indication.						
a) Cost per claim (e.g. doses per day, cost per dose, cost per day)						
b) ODB claims per year						
c) Total expenditures						
d) Net impact						

SECTION IV. CONTINGENCY ESTIMATES – PESSIMISTIC AND OPTIMISTIC SCENARIOS

For each parameter, it would be helpful to organize the data according to Baseline (where applicable), Year 1, Year 2, and Year 3 with the confidence level (high, medium or low) and the evidence/data sources.

Parameter	Baseline	Year 1	Year 2	Year 3	Confidence Level (high/med/low)	Evidence used to support assumptions
PESSIMISTIC SCENARIO (SUBMITTED PRODUCT PERFORMANCE IS BELOW EXPECTATIONS)						
Total annual ODB expenditure (submitted product) ($)						
Incremental change vs. most likely forecast ($)						
Total ODB expenditure (therapeutic class) ($)						
Incremental change vs. most likely forecast ($)						
Rationale for changes (list/identify any significant modifications in assumptions)						
OPTIMISTIC SCENARIO (SUBMITTED PRODUCT PERFORMANCE EXCEEDS EXPECTATIONS)						
Total annual ODB expenditure (submitted product) ($)						
Incremental change vs. most likely forecast ($)						
Total ODB expenditure therapeutic class) ($)						
Incremental change vs. most likely forecast ($)						
Rationale for changes (list/identify any significant modifications in assumptions)						

Template Written Agreement Letter

[Manufacturer's letterhead]

[Date]

Deputy Minister
Ministry of Health and Long-Term Care
10th Floor, Hepburn Block
80 Grosvenor Street
Toronto, ON M7A 1R3

Dear Deputy Minister:

REFERENCE: *[Product name/generic name, strength, and dosage form]*

(XYZ) agrees to follow the "New Drug Listing Evaluation" process agreed to by the Ministry of Health and the Pharmaceutical Manufacturer's Association of Canada set out in Schedule "A".

In consideration of having the above drug products listed on the ODB Formulary, and in accordance with the process noted above, (XYZ) agrees that the forecasted net cost to the province for the (#) of drug products for the three year period will be:

Year 1:
Year 2:
Year 3:

It is understood that the term "net costs" includes all amounts reimbursed for the drug product(s) under Sections 5 and 6 of the ***Ontario Drug Benefit Act*** (ODBA) and does not include amounts reimbursed for mark-up or dispensing fees, or for reimbursement of Section 8 approvals.

It is understood that nothing in this agreement shall limit the right of the Lieutenant Governor in Council to take any action as may be permitted under the current provisions of the ODBA and regulations made thereunder.

XYZ Corporation

Per: ____________________________
(Authorized Signing Officer)
(I have authority to bind the corporation)

Approved: ________________________
Deputy Minister

Date: ________________________

PART VII

NEW POLICY DIRECTIVES

From time to time, correspondence will be distributed to manufacturers outlining new policy directives undertaken by the Drug Programs Branch. This section is reserved for filing of information relating to the drug submission review process for easy reference.